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CLINICAL AND PATHOLOGIC DIFFERENTIATION OF THE ACUTE LEUKEMIAS

WITH SPECIAL REFERENCE TO ACUTE MONOCYTIC LEUKEMIA

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PEIPING, CHINA

Friedreich¹ in 1857 reported a case of leukemia with an acute course. Ebstein² in 1889 described the clinical picture of acute leukemia. Fraenkel³ in 1895 directed attention particularly to changes in the cells of the blood, and expressed the view that all acute leukemias were lymphogenous because of the similarity of the white blood cells of these patients to lymphocytes. Naegeli⁴ in 1900 described the myeloblast, thereby permitting, on the basis of the cytologic characteristics, the separation of two types of acute leukemia, myeloblastic or acute myelogenous and lymphoblastic or acute lymphatic. A sharp differentiation, however, was not always clear owing to difficulties in technic of staining blood smears and because of atypical cases which defied classification.

Further elucidation of the problem was forthcoming in the discovery by Reschad and Schilling-Torgau⁵ in 1913 of a third type of acute leukemia, acute monocytic leukemia. Although twenty years have elapsed since the appearance of this significant contribution, there have been only a few cases described. A recent review of the subject by Clough⁶ mentioned only twenty-three cases which he considered to be adequately described and acceptable. These were recorded in the medical literature by twenty different groups of investigators. Of the twenty-

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1. Friedreich, N.: Ein neuer Fall von Leukämie, *Virchows Arch. f. path. Anat.* **12**:37, 1857.

2. Ebstein, W.: Ueber die acute Leukämie und Pseudoleukämie, *Deutsches Arch. f. klin. Med.* **44**:343, 1889.

3. Fraenkel, A.: Ueber acute Leukämie, *Deutsche med. Wchnschr.* **21**:639, 663, 676, 699 and 712, 1895.

4. Naegeli, O.: Ueber rotes Knochenmark und Myeloblasten, *Deutsche med. Wchnschr.* **26**:287, 1900.

5. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenocytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, *München. med. Wchnschr.* **60**:1981, 1913.

6. Clough, P. W.: Monocytic Leukemia, *Bull. Johns Hopkins Hosp.* **51**:148, 1932.

three cases, all but six had been reported during the four years immediately preceding Clough's review, indicating that more and more cases were being recognized as the disease became better understood. During the past two years at the Thorndike Laboratory of the Boston City Hospital fifteen cases of acute leukemia in adults have been studied. Another case was studied in 1928. These sixteen cases have been equally divided between the three main types: myelogenous, lymphatic and monocytic. Postmortem examinations were made in four of the six cases of monocytic leukemia. One case of acute myelogenous leukemia and one of acute lymphatic leukemia with postmortem examinations of each are also recorded in this report as examples of the two other main types of acute leukemia.

The purpose of this report is to direct attention to certain clinical and pathologic features which appear to distinguish acute monocytic leukemia from the other forms of acute leukemia. The clinical and pathologic differences in this series of cases have been striking and of sufficient value to allow of a tentative diagnosis of acute monocytic leukemia independent of the studies on the blood. It seems reasonable to assume that a more general appreciation of the distinguishing features will result in the proper classification of many cases of acute monocytic leukemia which in the past have been unrecognized.

No attempt will be made to review the reported cases except to correlate certain features of these cases with those here reported. Adequate reviews of the disease have been published by Dameshek,⁷ Clough,⁸ and other physicians.

ACUTE MONOCYTIC LEUKEMIA

CASE 1.—*Medical History*.—W. C., a white man, aged 31, a professor, was admitted to the hospital complaining of soreness of the mouth and the throat.

His general health had always been good until about one and one-half years prior to admission, when he noticed that he became fatigued more easily than normal. This tendency had been more marked during the last few weeks before admission. He had had occasional occipital headaches for many years. He had always bruised rather easily. Scarlet fever and whooping cough occurred in childhood, but he had no other acute or chronic diseases. The family history was of no significance except that his mother died of pulmonary tuberculosis twenty-eight years previously.

The important features about the patient's dietary habits were that during the past few years he had eaten irregularly, often missing some meals entirely, owing to the nature of his work. Also he had always been very fond of dairy products, such as butter, cream, eggs and milk. He ate much more butter than the other members of his family, and felt that it was an important part of his food.

It was difficult to determine with certainty the onset of the present illness. The patient had been feeling a little under par for about eighteen months. Three

7. Dameshek, William: Acute Monocytic (Histiocytic) Leukemia, *Arch. Int. Med.* 46:718 (Oct.) 1930.

months before admission he acquired a superficial infection of two fingers which did not clear up as quickly as such infections usually do. One month before admission he contracted a cold with an irritating, but nonproductive, cough which gradually got better over a period of three weeks, but never completely disappeared. His appetite was good until the onset of the cold and then gradually became poorer.

Two weeks before admission the lower front teeth became loose and the gums painful. This was associated with painful swellings in the left side of the neck and with a sore throat. Three days before admission ulcers appeared in the region of the swollen gums. These presenting symptoms brought him to the hospital.

Examination.—The patient was a well developed and well nourished man with moderate pallor and with marked swelling of the left side of the face extending over the maxillary and mandibular areas. The skin showed a few scattered petechiae over the trunk and a fine powdering of small petechiae over the lower part of the legs. On the back of his left forearm was a hemorrhagic area in the center of which there was a blister 1 cm. in diameter which was not tender. A few subcutaneous, blue, hemorrhagic areas, presumably bruises, were found over the extremities. The eyes were normal except for slight retinal edema and a few scattered hemorrhagic areas with yellowish-white centers in the retina.

The breath was very offensive. The gums were swollen, and red. In some places they showed a purple discoloration and were soft. Ulceration was present about the margins of the gums, especially in the region of the upper molar and premolar teeth. Many of the teeth were loose. The tonsils were enlarged and reddened. Spirochetes and fusiform bacilli were present in the smears from the gums and tonsils. On the left side of the hard and soft palate there was an extensive submucous hemorrhage. The swelling of the left side of the face apparently was dependent on an extension of the infection from the mouth, presenting a picture of diffuse cellulitis.

The lymph nodes were generally moderately enlarged and slightly tender in the inguinal, axillary and cervical regions. Those in the cervical region measured from 1 to 2 cm. in diameter. A left epitrochlear lymph node was palpable.

The lungs were clear. The heart was within normal limits of size on percussion. The pulse rate was 110 per minute; the rhythm was regular. The blood pressure was 112 systolic and 60 diastolic.

The edge of the liver was palpable at the costal margin in the midclavicular line, and on percussion dulness in this line extended to the sixth rib. The edge of the spleen on full inspiration was felt 4 cm. below the costal margin. The abdominal muscles were somewhat rigid, and there was slight tenderness in the region of the spleen.

Neurologic examination revealed no abnormalities.

Laboratory Examinations.—Urinalysis showed: specific gravity, 1.015; sugar, none; albumin, a trace. The sediment contained numerous epithelial casts and a few leukocytes.

The Wassermann reaction of the blood serum was doubtful.

The nonprotein nitrogen of the blood was 76 mg. per hundred cubic centimeters. The coagulation time of the blood was twelve minutes by the method of Lee and White. The bleeding time was twenty minutes plus. The icteric index was 5 units. The blood cell count is shown in table 1.

TABLE 1.—Studies on the Blood Cells in Acute Leukemia

Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, per C.Mm.	Blood Platelets, Estimated or per C.Mm.	Nucleated Differential Leukocyte Formula							Mono- cytes of All Ages, per Cent	Lympho- Unclas- sified, per Cent	Comment
			Per Cent	Gm. per 100 Cc. Blood			Red Cells per 100 White Cells	Polymorphonuclear				Myelo- cytes of Various Types, per Cent				
								Neutro- phils, per Cent	Baso- phils, per Cent	Eosino- phils, per Cent	Myelo- cytes of Various Types, per Cent					
1 Acute monocytic leukemia	2/12/31	2.19	46	7.18	62,000	Marked decrease	...	0.5	0.5	...	0.5	...	94.0	4.5	...	94 per cent of cells contained fine oxidase granules
	2/13/31	2.23	47	7.33	92,500	Marked decrease	
	2/14/31	2.17	45	7.02	103,500	Marked decrease	...	2.5	...	3.0	1.5	...	87.5	5.0	0.5	
	2/16/31	1.75	39	6.08	72,500	Marked decrease	0.5	1.5	0.5	0.5	0.5	...	91.0	6.0	...	
	2/17/31	1.47	38	5.93	34,000	Marked decrease	...	1.0	1.0	...	94.5	3.0	0.5	
	2/18/31	1.69	32	4.99	124,500	Marked decrease	
	2/19/31	2.30	42	6.55	87,000	Marked decrease	
	2/20/31	2.02	39	6.08	103,000	Marked decrease	1.0	0.5	...	96.5	2.0	...	
	2/21/31	2.19	37	5.77	114,500	Marked decrease	0.5	1.5	...	96.0	2.0	...	
	2/22/31	1.90	41	6.40	77,500	Marked decrease	
	2/23/31	1.92	36	5.62	78,000	Marked decrease	
	2/24/31	1.97	35	5.46	87,000	Marked decrease	0.5	...	0.5	1.0	1.5	...	93.0	2.5	1.5	
2 Acute monocytic leukemia	2/27/31	1.96	40	6.24	97,000	Marked decrease	...	2.0	...	2.5	93.0	2.0	0.5	About 0.5 per cent of mono- cytes oxidase- positive
	3/ 2/31	1.59	33	5.15	150,500	Marked decrease	1.5	95.5	2.5	0.5	
	4/ 8/31	3.00	72	11.23	74,000	Marked decrease	
	4/ 9/31	19,500	Marked decrease	...	3.5	...	0.5	2.5	...	71.5	21.0	...	
	4/10/31	3.24	77	12.01	33,500	Marked decrease	0.5	2.0	81.0	17.0	...	
	4/13/31	3.54	79	12.32	60,500	Marked decrease	
	4/15/31	3.65	80	12.48	82,500	Marked decrease	...	1.5	89.0	9.5	...	
	4/17/31	2.56	62	9.67	172,000	Marked decrease	...	0.5	0.5	...	95.0	4.0	...	
	4/17/31	166,330	Marked decrease	...	0.5	92.0	7.5	...	
	4/18/31	2.85	51	7.96	364,000	118,000	...	0.5	95.5	4.0	...	

94 per cent of
cells contained
fine oxidase
granulesAbout 0.5 per
cent of mono-
cytes oxidase-
positive

Course.—The patient remained in the hospital for the last sixteen days of his life. No therapeutic measures that were tried were of any avail. Solution of potassium arsenite given by mouth seemed to be of no clinical value, although under such treatment the leukocytes decreased appreciably in number, but this effect was very transient. Three moderate doses of neoarsphenamine were given intravenously on Feb. 12, 16 and 24, 1931, but no improvement was apparent. Three transfusions of blood, each of 600 cc. of citrated blood given on February 19, 21 and 24, probably prolonged the patient's life for a few days. The local lesions of the mouth were treated with sodium perborate paste and solution and other cleansing washes which seemed to be of slight value. During the acute illness the temperature ranged from 100 to 103.5 F., and the pulse rate varied from 95 to 120 per minute. During the last few days of life bronchopneumonia of the middle lobe of the right lung, marked anemia, jaundice and signs of acute nephritis developed.

Postmortem Examination.—Gross Appearance: Petechial hemorrhages were present in the sclerae. The skin was markedly jaundiced. The mucous membranes of the buccal cavity, particularly those of the gums, were ulcerated, swollen and hemorrhagic. There was a generalized, discrete, pea-sized enlargement of the lymph nodes. One node in the left axilla measured 2.5 cm. in diameter. In the skin of the trunk and the extremities there were numerous small ecchymotic areas from 1 to 2 cm. in diameter. Over the insertion of the deltoid muscle in the right arm there was a hematoma 2 cm. in diameter with ecchymosis surrounding it for 3 cm. on all sides. There were numerous petechiae in the skin of the forearms and hands.

In the peritoneal cavity, the surfaces of the serosa, both parietal and visceral, were deeply jaundiced and full of petechial hemorrhages. All the adjacent surfaces throughout the cavity were adherent to each other by thin, filmy, yellowish strands simulating a very slight fibrinous exudate. These presented only slight resistance to separation of the surfaces affected. The domes of the diaphragm rose to the fourth interspace bilaterally. The edge of the liver was 9 cm. below the xiphoid process and 7 cm. below the costal margin in the midclavicular line. The spleen was much enlarged, and its lower pole was enveloped in the omentum. There were a few pea-sized, soft, grayish lymph nodes about the head of the pancreas and in the gastrohepatic ligament, but no palpable nodes in the mesentery.

There were petechiae and slight filmy adhesions in the pleural cavities.

The heart weighed 360 Gm. The myocardium was rather pale red and of normal consistence throughout; there was moderate hypertrophy of the left ventricle. There was slight fibrous thickening of the contact borders of the mitral valve.

The lungs were edematous and congested throughout. The lateral half of the right middle lobe was completely consolidated, quite firm and a grayish green, with a thick purulent exudate in the bronchioles. The hilar lymph nodes were slightly enlarged, soft and gray.

The spleen weighed 1,065 Gm. The capsule was thin and tense and varied in color from dark purple to red, in irregular blotches suggestive of capsular hemorrhages. The pulp was very soft and friable and dark brick red, with prominent trabeculae. The cut surface bulged on section and scraped away easily on the blade of the knife. There were several irregular lobulations around the hilus and lower pole that suggested accessory lobes.

The contents of the gastro-intestinal tract were dark greenish or a tarry color. There were multiple petechial hemorrhages throughout the mucosa from the

stomach to the end of the colon, but there was no evidence of frank hemorrhage from any single bleeding point. Bile flowed freely from the duodenal papilla.

The pancreas was very firm and hard throughout, but otherwise was normal.

The liver weighed 2,685 Gm. The surface was symmetrical, enlarged, smooth and gray. On section the liver was rather pale and firm in consistence, with prominent, slightly yellow, lobular markings, but there was no evidence of increased fibrous tissue. The gallbladder and bile ducts were normal.

The kidneys weighed 550 Gm. The fatty capsule was of a curious leathery consistence. The true capsule stripped readily, exposing a smooth pink surface. The renal tissue was soft and friable and on section appeared somewhat yellow. The cortex averaged fully 1.2 cm. in thickness; the pyramids were injected. The renal substance bulged on section. The calices contained a few small bits of orange gravel-like material and small blood clots. Otherwise, the pelves and the ureters were normal.

The suprarenal glands appeared to be normal.

The mucosa of the bladder was full of petechiae; otherwise the bladder was normal.

The genital organs were normal.

The aorta was slightly yellow, with soft atheromas.

The bone marrow was grayish pink and hyperplastic throughout.

The anatomic diagnosis was: leukemia; bronchopneumonia; acute pharyngitis; possibly acute nephritis; polyserositis (possibly fibrinous).

Microscopic Appearance: In the heart there were a few areas of focal infiltration of fat tissue with cells resembling monocytes, frequently showing mitoses.

There was marked edema of the lungs, with hemorrhages into the alveoli. Many alveoli were filled with monocytes, unclassifiable mononuclear cells and polymorphonuclear neutrophils in a network of fibrin. The alveolar walls were thickened by infiltration, with similar collections of cells. Many monocytes were filled with pigmented material.

The pulp of the spleen was densely infiltrated with large mononuclear cells, some with plentiful acidophilic, finely granular cytoplasm and large vesicular nuclei, others with a smaller amount of acidophilic cytoplasm and irregular vesicular nuclei. There were numerous mitoses in these cells; a few appeared to be multinucleated. Some of the larger cells appeared to have been phagocytic and contained granules, vacuoles, pigment and apparently red cells in the cytoplasm. The normal structure of the spleen appeared to be almost entirely obliterated.

There were foci of dense infiltration in the periportal tissue and in aberrant areas of the hepatic substance, with fibrin and cells similar to those described in the spleen except that large phagocytic monocytes were not present.

The stroma of the pancreas was everywhere densely infiltrated with the type cells.

The interstitial tissues of the kidneys, especially in the pyramids, were densely infiltrated with the cells described. No macrophages were present.

The perisuprarenal fat and fibrous tissue were densely infiltrated with monocytes and younger cells, as described in the spleen.

The structure of the lymph nodes was almost obliterated by dense infiltration with monocytes and younger forms.

The predominant cell in the bone marrow was a mononuclear cell with slight acidophilic cytoplasm and a fairly clear, vesicular nucleus. Many of the cells showed U-shaped nuclei. The macrophages were numerous and contained golden brown pigment and clear vacuoles. The majority of the cells were undoubtedly

monocytes. The formation of red cells was depressed. There seemed also to be a definite decrease in cells of the granulocytic series.

The microscopic diagnosis was monocytic leukemia.

CASE 2.—*Medical History*.—H. C., a white man, aged 38, married, a salesman, entered the hospital complaining of a sore mouth and weakness.

He was perfectly well until one month before admission, when he first noticed that his gums seemed more tender than usual and that they bled after brushing the teeth. He also noticed that he felt unusually tired after ordinary activities. A dentist was consulted; he made a diagnosis of "trench mouth" and gave the patient a mouth wash containing phenol, under which treatment the symptoms grew more intense. Smears from the gums were said to have been negative for pathogenic organisms. The patient was then seen by his physician; he found that the patient had slight anemia and gingivitis. Rest in bed and a diet consisting of liver and green vegetables were prescribed. Under this treatment his condition became worse, the gums became greatly swollen, he was feverish, and the weakness increased.

Two weeks before admission the patient had a dull ache across the sacrum and at the back of the head. This pain was transient, lasting a few hours, but recurred several times during the two weeks before admission.

Until one week before admission he worked steadily, driving an automobile about 200 miles a day. Two days before entering the hospital another physician was consulted; he found Vincent's organisms in the mouth and discovered that the patient had a high leukocyte count with many immature cells in the blood.

The past history was irrelevant. The patient had always been healthy and strong except for scarlet fever, chickenpox, measles and whooping cough in childhood.

The family history was of no importance except that one brother with whom the patient had been associated many years before had died of pulmonary tuberculosis.

The dietary history was of interest in that the patient had always eaten generously of fat, particularly cream and butter. His work as a traveling salesman had resulted in irregularity of meals, and frequently his food had been of poor quality. He was fond of vegetables and of meat and usually ate red meat and fresh vegetables at least once each day. He ate very little pastry or sweet foods. He smoked ten or twelve cigars a day and exercised very little.

Examination.—The patient was a well developed and well nourished man lying comfortably in bed without apparent discomfort. The skin, eyes, nose and ears were normal. The mucous membranes were slightly pale. The breath was very foul. The gums showed marked reddening and were greatly swollen or hypertrophied in some places, almost obscuring the sides of the teeth. At the back of the left central incisor tooth in the upper jaw was an area of necrosis, smears from which showed numerous fusiform bacilli and spirochetes. The tonsils were large, red and ragged. The pharynx was generally reddened. The tonsillar and submental lymph nodes were enlarged, measuring about 2 cm. in diameter. They were discrete and of moderately firm consistence, but not tender. The lymph nodes along the anterior borders of the sternocleidomastoid muscles, in the supraclavicular fossae and in the axilla, were similarly enlarged. A right epitrochlear lymph node was barely palpable. No lymph nodes could be felt in the pelvis, and those in the inguinal and femoral regions appeared to be normal.

The heart was slightly enlarged. The sounds were of good quality; the rhythm was regular, the rate being 86 beats per minute. There was a short soft systolic

murmur over the whole precordium. The blood pressure was 140 systolic and 64 diastolic. The lungs were normal to physical examination.

The spleen could be felt just below the costal margin, and was not tender. The edge of the liver extended 6 cm. below the costal margin in the midclavicular line. No other abnormalities were found.

Rectal examination revealed a tight sphincter and what appeared to be a small thrombosed external hemorrhoid which was moderately tender.

Examination of the genitalia, extremities and central nervous system revealed no abnormalities.

Laboratory Examinations.—The blood cell count and hemoglobin values are given in table 1.

The urine was yellow and acid, with a specific gravity of 1.012. There was no sugar, acetone or diacetic acid, but a slight trace of albumin. The sediment contained occasional hyaline and fine granular casts.

The nonprotein nitrogen of the blood was 28 mg. per hundred cubic centimeters. The icteric index of the blood serum was 10.6 units. A blood culture showed no growth. The bleeding time was four and one-half minutes. The coagulation time was twenty-four and one-half minutes (method of Lee and White).

The basal metabolic rate was +46 per cent.

Course.—Soon after admission solution of potassium arsenite was given by mouth for nine days, beginning with doses of 5 minims (0.3 cc.) three times a day and increased to 8 minims (0.5 cc.) three times a day. The number of leukocytes decreased, but the general condition of the patient grew worse, so that this medication was discontinued. Six days after admission the patient complained of severe pain in the rectum associated with defecation. Examination revealed swollen mucous membranes with a few nodular areas just within the anal sphincter. The rectum was dilated and one of the nodules excised for microscopic examination. The report of the pathologist was as follows: "A small nodule from the rectum showing infiltration with medium-sized cells with fairly numerous mitotic figures. The specimen is consistent with leukemic infiltration."

The necrosis of the gums increased, the anemia progressed, and the number of immature leukocytes in the blood became greater. The temperature, which on admission varied from normal to 100 F., increased to 102.5 F. Several days before death numerous petechiae appeared over the trunk and extremities and in the mucous membranes of the mouth and eyes. In spite of supportive treatment, the patient became weaker, râles developed in the bases of both lungs, and he died ten days after admission.

Postmortem Examination.—Gross Appearance: There was slight swelling of the lymph nodes in the left axilla to external palpation, but the others were not enlarged. There was no pitting edema. Scattered over the abdomen, especially in the left flank, were several bluish purpuric spots. At the left corner of the upper lip was a red-stained abrasion.

There was no free fluid in the peritoneal cavity. The peritoneal surfaces were smooth, glistening and without exudate. There were numerous subserous purpuric spots scattered over the visceral and parietal peritoneum. On the right, the diaphragm rose to the level of the third interspace, and on the left, to the fifth rib. The liver was 4 cm. below the xiphoid process and 4 cm. below the costal margin in the midclavicular line. The mesenteric lymph nodes were not enlarged.

There was a moderate amount of free, straw-colored, clear fluid in the left pleural cavity, but none in the right. A few easily broken adhesions bound both lungs to the posterior wall of the thorax. There was no fresh exudate.

There was a slightly increased amount of clear bloody fluid in the pericardial cavity, probably from a pericardial puncture performed shortly ante mortem. There were no adhesions.

The heart weighed 498 Gm. The myocardium was soft and of a grayish-red tinge, but showed no scarring. The valves showed no thickening or growths, and the endocardium was smooth. There were no antemortem clots. The coronary vessels everywhere were patent and without sclerosis.

The lungs were normal in size and shape and reddish gray. They were crepitant throughout without patches of consolidation. There was no pus. The vessels were patent. The hilar lymph nodes were slightly enlarged.

The spleen weighed 606 Gm. It was markedly enlarged, firm and gray-purple, with a smooth capsule. On section the pulp was a dark gray-red and appeared swollen; it tended to "round up" from the cut surface. No discrete follicles were observed. The surface scraped away rather easily.

The stomach and intestinal tract showed petechial hemorrhages throughout. The rugae of the stomach were not swollen. Peyer's patches of the ileum appeared to be normal. Masses could be felt in the rectal mucosa.

The pancreas was normal.

The liver weighed 2,670 Gm. It was markedly enlarged, brownish yellow, smooth on the surface and firm, with a rounded lower edge. On section the cut surface was yellow-brown, with dark brown mottling of the nutmeg type. The surface tissue was firm in consistence and could not be scraped away. The gall-bladder was normal.

The kidneys weighed 340 Gm. The capsule stripped with ease and revealed a grayish-purple, mottled, smooth surface. The cortex and medulla were slightly injected. The cortex showed no scarring or reduction in size, measuring on the average 7 mm. in thickness. There were no other abnormalities.

The suprarenal glands were normal.

The bladder was distended with clear, dark amber urine; otherwise, it was normal.

The penis was partially erected.

The aorta was normal.

Bone marrow taken from the fourth left vertebra was red and of normal consistence. Several ribs that were removed failed to show gross evidence of the areas of softening which had been recorded on roentgen examination. A small piece of bone from the greater trochanter of the left femur showed slight yellowish softening. Marrow from the cavity of the left femur was yellow and fairly firm.

The axillary nodes were enlarged, 3 by 2 by 2 cm., soft and gray-red. The lymph nodes at the bifurcation of the aorta and along the iliac arteries were moderately enlarged, soft and a grayish purple.

There were marked swelling and areas of necrosis in the gums.

The anatomic diagnosis was: generalized enlargement of the spleen, liver and lymph nodes; multiple petechial hemorrhages; hydrothorax, left; pulmonary edema and congestion; old pleuritis; gingivitis.

Microscopic Appearance: There was diffuse cellular infiltration of the muscle of the heart with cells, for the most part from 10 to 12 microns in diameter, with round, slightly indented, fairly deeply staining nuclei with a fine chromatin network and with thin circular veins of even neutrophilic cytoplasm. Most of the cells contained irregular, lobulated nuclei. There were occasional mast cells. The

vessels were filled with infiltrating cells. There was slight Zenker's degeneration of the muscle of the heart.

There was infiltration of the capillaries of the lungs with type cells. The alveoli were partially filled with serum, type cells, red blood cells and occasional fibrin precipitate.

In the spleen there was diffuse infiltration with type cells, both within the vessels and in the pulp. There were focal areas of necrosis. One multinucleated giant cell was seen. There were no typical megakaryocytes. Fibrin was present throughout.

The liver was infiltrated with type cells, especially in the periportal areas. There was fatty degeneration of the cells in the central zones, with necrosis of a few cells in the same regions. There were occasional cells that resembled nucleated erythrocytes. The oxidase reaction of the infiltrating cells was negative.

The kidneys showed infiltration of the glomerular tufts and the subcapsular, periglomerular and intertubular areas by type cells. There was slight tubular dilatation.

There were type cells in the vessels and perivascular spaces of the pancreas, with a few cells infiltrating the pancreatic substance.

The suprarenal glands showed diffuse infiltration by type cells. There was slight lumen formation.

The aorta showed infiltration of the adventitia and media by type cells.

The testes showed infiltration of the stroma by type cells.

The vessels of the submucosa of the stomach were filled with type cells. The tunica propria beneath the glands was infiltrated with type cells.

The lymph nodes had lost their normal structure. There was diffuse infiltration with type cells. There was an occasional cell resembling a nucleated red corpuscle. The adjacent blood vessels were filled with type cells. Monocytes phagocytosing lymphocytes and type cells were seen. There were no megakaryocytes.

The femoral bone marrow showed diffuse infiltration by type cells. Focal areas, which stained red, consisted of many red blood cells, and there was a more eosinophilic staining of the type cells themselves. There were many nucleated red blood cells which showed fragmentation of the nuclei.

In the bone marrow from the greater trochanter there were bits of bone without nuclei which took a heavy basophilic stain. There were a few type cells in the marrow.

The vertebral bone marrow showed diffuse infiltration of the marrow cavity by type cells, the nuclei of which stained more deeply and the cytoplasm of which was more bluish than elsewhere.

The microscopic diagnosis was monocytic leukemia.

Postmortem Culture.—A culture of blood from the heart showed no growth.

CASE 3.—Medical History.—S. W., a man, aged 40, single, a Polish laborer, entered the hospital on Oct. 23, 1931, complaining of headache, toothache and bleeding from the mouth.

The patient was perfectly well until about six weeks before admission, when it was noticed that his gums began to bleed slightly after brushing the teeth and after chewing hard foods. Also at this time it was noticed that the slightest injury caused the appearance of black and blue spots in his skin. These signs were not accompanied by any general discomfort, but gradually increased in intensity. The gums became swollen and tender.

Five days prior to admission severe aching in the region of the second left upper molar tooth occurred, accompanied by a generalized, dull, persistent headache. Two days before admission the patient consulted a dentist; he extracted the tooth. Extensive bleeding persisted for twelve hours in spite of packing. The patient estimated that about 2 quarts of blood had been lost. During the night there was slight continued oozing of blood. The next morning, one day before admission, he felt very weak and was unable to get out of bed. The aching subsided but the gums remained very tender.

The past history and family history were not significant. Nine years before admission an operation was performed for hemorrhoids. One year prior to the present illness the patient had been successfully treated for gonorrheal urethritis. He remembered no other illnesses. During the past six years he had severe constipation and had taken two compound cathartic pills practically daily. Without such medication his bowels would not move, and this condition was associated with frequent headaches.

The dietary history was important in that the patient ate very irregularly, and the quality of the food was usually poor. Rarely did he have fresh vegetables or fruit, except tomatoes, which he ate in large quantities. He drank moderately of poor quality alcohol or whisky about twice a week.

He had lost about 20 pounds (9 Kg.) during the last two years.

Examination.—The patient was a well developed and well nourished middle-aged man who looked pale, worn and apprehensive. There were obvious moderate swelling and redness of the whole left side of the face, more marked in the infra-orbital region. This area was moderately tender but not fluctuant. There were numerous small petechiae over both inguinal regions, the chest and the back. Several ecchymoses were present, from 2 to 3 cm. in size and irregular in contour, over the upper part of the right arm and the lower part of the left leg.

Except for some swelling of the lower lid of the left eye, the eyes were normal to routine physical and ophthalmoscopic examinations. The ears and nose were normal.

The breath was very foul. There was a large ulcerated area in the gums of the left side of the upper jaw, at the site of the extraction of the tooth. The margins of the ulcer, the buccal mucous membrane and the soft palate were hemorrhagic. Spirochetes and fusiform bacilli were present in a smear from the ulcerated area. There were several hemorrhagic vesicles on the lips on the left side. The teeth were dirty, but showed no obvious caries. The gums were generally hypertrophied and spongy. The tonsils were hypertrophied, but showed no evidence of acute infection except diffuse redness, which was present throughout the pharynx. The lymph nodes in the neck and right epitrochlear region were slightly enlarged. One lymph node, 1.5 cm. in diameter, in the left submaxillary region was tender, firm and freely movable.

The heart and lungs were normal on physical examination. The pulse rate was regular and of good quality. The blood pressure was 118 systolic and 70 diastolic. The spleen and liver were not palpable. There were no masses, spasm or tenderness in the abdomen. Examination of the bones and neuromuscular systems revealed no abnormalities except for absence of the abdominal reflexes.

Laboratory Examinations.—The results of studies on the blood are shown in table 2. The bleeding time was twenty-four minutes; the coagulation time, four minutes. The blood belonged to group IV (Moss classification). The Wassermann reaction of the blood was positive. A blood culture was negative in aerobic and anaerobic mediums.

TABLE 2.—Studies on the Blood Cells in Acute Leukemia

Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, C.Mm.	Blood Platelets, Estimated or per C.Mm.	Nucleated Differential Leukocyte Formula										Mono- cytes of All Ages, per Cent	Lympho- cytes, sified, per Cent	Unclas- ified, per Cent	Comment
			Per Cent	Gm. per 100 Cc. Blood			Red	Polymorphonuclear		Baso- phils,		Eosino- phils,		Myelo- cytes of Various Types,		Myelo- cytes per Cent				
								Cells per 100 C.C.	Cells per Cent	Cells per Cent	Cells per Cent	Cells per Cent	Cells per Cent	Cells per Cent	Cells per Cent					
3 Acute monocytic leukemia	10/22/31	4.00	80	12.48	83,500	Marked decrease		
	10/23/31	3.70	80	12.48	82,500	Marked decrease	0.5	2.0	96.0	1.0	1.0		
	10/26/31	3.84	78	12.17	72,000	Marked decrease	...	5.0	92.0	3.0	...		
	10/29/31	3.65	74	11.54	82,250	Marked decrease	0.5	2.5	...	0.5	96.5	0.5	...		
	10/31/31	3.34	70	10.92	87,000	Marked decrease	...	4.0	0.5	93.0	1.5	...		
	11/ 2/31	3.35	65	10.14	93,500	Marked decrease	0.5	3.0	1.0	95.0	1.0	...		
	11/ 5/31	3.38	60	10.30	95,000	Marked decrease	2.0	3.0	95.0	2.0	...		
	11/ 6/31	3.49	05	10.14	121,000	Marked decrease	1.0	6.0	3.0	90.0	1.0	...		
	11/ 7/31	3.52	04	9.98	119,500	Marked decrease	0.5	2.0	85.0	3.0	...		
	11/ 9/31	3.12	60	9.36	148,500	Marked decrease	...	9.0	2.0	86.0	2.0	1.0		
	11/10/31	3.06	56	8.74	169,500	Marked decrease	...	2.0	1.0	95.0	2.0	...		
	11/12/31	2.61	50	7.80	125,500	Marked decrease	1.0	3.0	96.0	1.0	...		
	11/13/31	2.46	50	7.80	73,000	Marked decrease	0.5	1.5	98.0	0.5	...		
	11/14/31	2.86	32	8.11	130,500	Marked decrease	1.0	2.0	97.0	1.0	...		
	11/16/31	2.56	50	7.80	140,500	Marked decrease	...	2.0	98.0		
	11/18/31	2.23	49	7.64	160,500	Marked decrease	5.0	4.0	95.0	1.0	...		
	11/19/31	2.42	50	7.80	242,000	Marked decrease		
	11/20/31	2.48	49	7.64	143,500	Marked decrease	4.0	5.0	93.0	2.0	...		
	11/21/31	2.14	122,000	Marked decrease	3.0	5.0	89.0	6.0	...		
	11/23/31	1.80	39	6.08	140,000	Marked decrease	3.0	2.0	2.0	95.0	1.0	...		
	11/24/31	1.90	39	6.08	169,500	Marked decrease	3.0	2.0	1.0	96.0	1.0	...		
	11/27/31	1.72	40	6.24	234,000	Marked decrease	19.0	4.0	95.0	1.0	...		

Almost all cells
oxidase-posi-
tive

The urine was yellow and acid, with a specific gravity of 1.015. It contained a trace of albumin. Tests for sugar, acetone and diacetic acid were negative. The sediment contained a few white blood cells and an occasional red blood cell.

Gastric analysis showed no free hydrochloric acid in the contents taken during fasting or in those taken after an alcohol meal. The combined acid was 14 units.

The stool contained no ova or parasites. The guaiac test was negative.

A roentgenogram of the chest showed normal pulmonary fields.

Course.—During the first few days after admission to the hospital, the patient's general condition greatly improved with rest in bed and local treatment of the ulcerated lesions. The swelling of the face subsided, the ulcer became smaller, and the temperature, pulse rate and respiratory rate were reduced to normal. In spite of this improvement, the red blood cell and hemoglobin values greatly decreased.

One week after admission there was further bleeding from the gums, which recurred at intervals. Two weeks after admission pain and swelling recurred in the left maxillary region, and there was edema of the pharynx. The fever increased to 101 F., and the pulse rate to 110 beats per minute. A blood culture was again negative. On November 7, solution of potassium arsenite was given by mouth, beginning with doses of 5 minims three times a day, gradually increasing until November 21, when the patient was taking 11 minims (0.68 cc.) three times a day. No significant change occurred in the number or character of the white blood cells. The anemia progressed, and the general condition grew worse. There was evidence of consolidation in the bases of both lungs; this observation was confirmed by roentgen examination. The patient died on November 28, five weeks after admission.

Postmortem Examination.—Gross Appearance: The body was that of a well developed, but only fairly well nourished, white man showing slight rigor mortis and slight dependent lividity. The condition of the pupils could not be made out because of the shrunken condition of the eyelids. Over the lateral aspect of both arms and over the cubital space there were bluish areas representing puncture marks. Over the body generally there were small red petechial areas. There was clotted blood in both nostrils and ears and in the mouth. The axillary, cervical and inguinal lymph nodes were somewhat enlarged.

There was no increase of fluid in the peritoneal cavity. The peritoneum, particularly that covering the intestine, was dull, granular and slightly reddened. Small strands of fibrin could be peeled from these areas. The edge of the liver extended 8 cm. below the xiphoid process and from 3 to 4 cm. below the right costal border at the midclavicular line. The diaphragmatic domes were on a level with the fourth rib on the right and the fourth interspace on the left.

Both pleural cavities contained about 400 cc. of pure blood, most of which was not coagulated.

The surfaces of the pericardial cavity were normal, but the cavity contained 150 cc. of blood-tinged fluid.

The heart weighed 380 Gm. It was slightly increased in size and very flabby. The epicardium was smooth and the myocardium, pale red; the endocardium and valves were normal.

The lungs were covered with clotted blood. The posterior portion of each had diminished crepitus. Section showed a reddened parenchyma, particularly in the dependent portions. There was congestion throughout. On pressure a rather thick blood-stained fluid exuded.

The spleen weighed 360 Gm. It was enlarged and very soft. Section showed a soft reddish parenchyma the markings of which were very indistinct. Scattered throughout were small gray foci. The pulp scraped off easily.

The small and large intestines were considerably discolored; the mucosa was normal.

The liver weighed 2,200 Gm. The surface was smooth and pale gray-yellow. Section showed a parenchyma which for the most part appeared rather homogeneous. There were a few irregular areas with a slightly pink tinge. The consistence was normal. Bile flowed freely from the ampulla of Vater.

The kidneys weighed 460 Gm. Both organs were large and pale gray. Section showed a pale gray parenchyma. The pyramids and cortex were distinct. In the pelvis of each kidney there was blood, most of which was clotted. The ureters were normal.

The suprarenal glands, pancreas, bladder, genital organs and aorta were normal.

The lymph nodes of the axillary and cervical regions and of the groin were moderately enlarged, the largest measuring 3 cm. in diameter. The nodes were soft and on section showed a gray, soft parenchyma.

The bone marrow taken from the femur was fatty; that taken from the sternum and vertebra was paler than normal.

The anatomic findings were consistent with leukemia and hemothorax; there was a question as to whether bronchopneumonia had been present.

Microscopic Appearance: The microscopic changes in this case were similar to those in the two previous cases in that there was rather marked infiltration of the viscera with type cells. The type cells in this case were not as typical of monocytes as in the previous cases. The character of the cells was similar except that the nuclei for the most part were oval or round instead of elongated, folded or otherwise irregular. This suggested the possibility of the cells being myeloblasts or early myelocytes rather than monocytes. However, study of the blood during life, by means of the supravital technic, convinced me that the abnormal cells belonged to the monocytic strain. The oxidase reaction of the abnormal cells in the tissues, as in the blood, was positive, but the granules were fewer and finer than those usually encountered in early myelocytes.

The bone marrow, lymph nodes and spleen, as in the previous cases, were hyperplastic, with almost complete obliteration of the normal architecture.

The microscopic diagnosis was acute leukemia, probably monocytic.

CASE 4.—Medical History.—E. L., a white man, aged 26, married, a telephone lineman, came to the hospital with the complaint of ulcerated, bleeding gums and general weakness.

An accurate history was unobtainable in that the patient was in a critical state on admission, from which he made no recovery.

About two weeks before admission the patient complained of severe toothache. A dentist was consulted; he extracted two upper incisor teeth. This was followed by profuse hemorrhage for several hours, which was finally checked by packing the bleeding cavities with gauze. Although the patient had felt quite well until the onset of the toothache, from this time on he became progressively weaker. Eight days after extraction he became acutely ill and had a high fever.

The past history could not be obtained in detail. It was learned that for the past two years, following an appendectomy, the patient had not felt as strong as previously, and had suffered from recurrent attacks of abdominal pain.

Examination.—The patient was a well developed and well nourished man in a semicomatose state, markedly dyspneic and cyanotic; he frequently spat up bright blood. He occasionally opened his eyes and answered simple questions.

The skin was moist and hot, but there were no petechiae, ecchymoses or other lesions of the skin. The mucous membranes were pale and cyanotic.

Examination of the ears, nose and eyes revealed no abnormalities. No hemorrhages or areas of leukemic infiltration were present in the fundus.

The breath was very foul; the gums were ulcerated and gangrenous. There was clotted blood over the teeth and gums. The lips were cyanotic. The teeth were in fair condition, except for two upper incisors, which had recently been extracted; the cavities were filled with clotted blood. There were a few petechiae in the mucous membranes of the hard and soft palate and of the cheeks. The tonsils were not enlarged.

In the neck the lymph nodes were moderately enlarged, from 0.5 to 2 cm. in diameter. The lymph nodes in the axillae and groins also were moderately enlarged. There was definite but slight dulness over the bases of both lungs, together with suppression of breath sounds. No râles or rûbs were heard. The rate of respiration was 30 per minute. Aside from a soft systolic murmur at the apex and some accentuation of the aortic second sound, the heart was normal on examination. The spleen was felt 3.5 cm. below the costal margin. Its edge was rounded and only moderately firm. The liver extended 4 cm. below the costal margin in the midclavicular line and was not tender. No other masses or tenderness was found. Examination of the extremities and of the neuromuscular system revealed no abnormalities.

The history and physical findings in this case were so similar to those of the three previous cases that a tentative diagnosis of acute monocytic leukemia was made before the blood was actually examined.

Owing to the patient's critical condition on admission, he was given a transfusion of 600 cc. of citrated blood. There was no untoward reaction, and no improvement followed. Later in the same day bronchial breathing was heard over the upper portion of the lower lobe of the left lung. The patient died twenty-five hours after admission.

Laboratory Examinations.—The results of studies on the blood are shown in table 3. The nonprotein nitrogen of the blood was 40 mg. per hundred cubic centimeters; the blood sugar, 80 mg. The bleeding time was prolonged. The Wassermann reaction of the blood was negative. A blood culture showed pneumococcus, type 18.

The urine was yellow, acid and cloudy; the specific gravity was 1.010. It contained a trace of albumin, granular and hyaline casts and an occasional white blood cell; sugar was not present.

Postmortem Examination.—Gross Appearance: The body was that of a well developed and well nourished white man. There were very slight rigor mortis and slight dependent lividity. Edema was not present. There were tattoo marks on the right forearm, and the scar of a lower right rectus incision was seen in the abdominal wall. A few small firm lymph nodes about 1 cm. in diameter were palpable in both inguinal regions. The other superficial lymph nodes were not palpable.

The peritoneal cavity contained no free fluid. There were a few old fibrous adhesions about the abdominal wound in the cecal region. The appendix was absent. The mesenteric lymph nodes were moderately and uniformly enlarged; those at the root of the mesentery averaged about 1.5 cm. in diameter. They were soft, uniform and pinkish gray on the cut surfaces. The diaphragm extended to the fifth space on the right and to the sixth rib on the left.

TABLE 3.—Studies on the Blood Cells in Acute Leukemia

Nucleated Differential Leukoocyte Formula																
Case and Diagnosis	Date	Red Blood Cells, Millions per C.Mm.	Hemoglobin		White Blood Cells, per C.Mm.	Blood Platelets, Estimated or per C.Mm.	Red Blood Cells per 100 White Blood Cells	Polymorphonuclear					Mono- cytes of All Ages, per Cent	Lympho- cytes, Unel- as- sified, per Cent		Comment
			Per Cent	Gm. per 100 Cc. Blood				Neutro- phils, per Cent	Baso- phils, per Cent	Eosino- phils, per Cent	Myelo- cytes of Various Types, per Cent	Myelo- blasts, per Cent		Lympho- cytes, per Cent	Unel- as- sified, per Cent	
4. Acute monocytic leukemia	9/11/31	3.24	54	8.42	52,700	Very few	...	5.0	7.0	...	77.0	7.0	4.0	From 85 to 95 per cent of cells oxidase-positive
	9/12/31	4.16	54	8.42	73,500	Very few	3.0	9.0	8.0	...	81.0	2.0
	10/13/31	2.10	160,000	Very few	25 per cent of abnormal cells with many fine oxidase gran- ules; 50 per cent of abnormal cells with few fine oxidase granules; 25 per cent of abnormal cells oxidase- negative
	10/15/31	1.60	36	5.62	128,000	Very few	...	8.0	75.0	17.0
	10/19/31	1.81	33	5.15	110,500	Very few	...	2.0	1.0	...	94.0	3.0
5 Acute monocytic leukemia	10/23/31	74,200	Very few
	10/31/31	0.90	15	2.34	104,000	Very few	...	25.0	67.0	8.0
	12/17/28	1.61	50	7.80	71,000	Marked decrease	...	8.0	6.0	...	70.0	16.0
	12/18/28	1.65	73,750	Marked decrease	1.6	19.0	9.0	...	65.0	4.0
	12/21/28	1.71	40	6.24	93,400	Marked decrease	...	7.0	1.0	...	79.0	13.0	...	No oxidase stains used
6 Acute monocytic leukemia	12/22/28	2.00	45	7.02	99,800	Marked decrease	...	6.0	3.0	...	82.0	9.0
	12/23/28	1.84	45	7.02	110,000	Marked decrease	...	2.0	1.0	...	88.0	10.0
	1/14/31	0.83	20	3.12	121,000	Absent	0.5	1.5	3.5	92.0	0.5	2.0	0.5	27 per cent of cells contained a few large oxi- dase granules
7. Acute myelogenous leukemia	1/15/31	0.77	194,000	Absent
8 Acute lymphatic leukemia (leukosarcoma)	1/28/31	3.07	51	7.96	1,110,000	Very few	...	1.5	0.5	98.0	...	All lympho- cytes oxidase- negative
	1/29/31	2.74	53	8.27	920,000	Very few
	1/30/31	3.01	53	8.27	795,000	Very few	0.5	0.75	0.5	98.75

The pleural cavities contained no free fluid. The parietal pleura was not examined because of restriction.

The pericardial cavity and the heart were not examined because of restriction. The heart was not enlarged to palpation.

The lungs weighed 1,530 Gm. They were crepitant throughout save for an area about 5 cm. in diameter in the upper posterior part of the lower lobe of the left lung. On cut surface this area was poorly demarcated, grayish red and drier than the surrounding lung. In addition there were scattered patches of consolidation from 0.5 to 1 cm. in diameter throughout both lungs.

The spleen weighed 900 Gm. It was markedly enlarged. The cut surface was uniformly grayish red and rather dry.

The small lymph nodes close to the mesenteric attachment were uniformly moderately enlarged. Peyer's patches did not appear to be enlarged. The gastrointestinal tract was otherwise normal throughout.

The pancreas was normal.

The liver weighed 2,900 Gm. It was considerably enlarged, and extended 12 cm. below the xiphoid process and 8 cm. below the costal margin in the mid-clavicular line. The surface was smooth, and the lobulation was rather prominently visible through the capsule. The cut surface was paler than normal, with slightly accentuated markings. The consistence was normal.

The kidneys weighed 720 Gm. and were considerably enlarged. The right pelvis and ureter were moderately dilated, but no anatomic cause could be discovered. The capsules stripped readily, leaving a smooth surface. The cut surface was pale, and the renal substance showed marked streaking and mottling with yellowish-white tissue.

The medulla of the suprarenal glands was liquefied. The cortex appeared normal.

The bladder was distended with about a liter of clear urine, but was otherwise normal.

The genitalia appeared to be normal.

The aorta was elastic and normal throughout.

The vertebral marrow was very hard, calcified and a uniform grayish pink.

The anatomic diagnosis was: bronchopneumonia; generalized lymphatic enlargement; splenomegaly; enlargement of the liver and kidneys; cellular infiltration of the bone marrow; hydronephrosis, right. The anatomic findings were consistent with leukemia.

Microscopic Appearance: No sections of the heart were taken.

The alveoli of the lungs throughout were filled with coagulated serum, leukocytes, occasional hemorrhage and irregular masses of fibrin, chiefly around the bronchi. The leukocytes were chiefly monocytes. In addition, there were many very large cells with single or multiple vesicular nuclei and cytoplasm filled with very finely granular brown pigment. The bronchioles were filled with plugs of fibrin and leukocytes, showing a predominance of mononuclears. The intervalveolar capillaries were congested and contained large numbers of monocytes.

The lymphoid nodules of the spleen were crowded out, and the pulp spaces were distended by large numbers of mononuclear cells. Many of the larger mononuclears contained masses of brown pigment and partly digested red blood cells. Occasional megakaryocytes were present in the pulp. The endothelium of the larger arteries was lifted from the media by a considerable accumulation of monocytes.

The portal spaces of the liver contained many lymphocytes and mononuclear cells. The sinusoids were uniformly distended with large numbers of mononuclear cells. There were a few small areas of subintimal infiltration in the large veins.

The pancreas was normal save for large numbers of mononuclear cells in the vessels.

There was an occasional small accumulation of mononuclear cells in the stroma of the cortex and medulla of the kidneys. Moderate hydropic swelling of the epithelium of the convoluted tubules was noted. Like the vessels elsewhere, the glomerular capillaries contained many mononuclear cells.

There was very marked lipoid disintegration of the zona fasciculata of the suprarenal glands. There was a marked diffuse accumulation of lymphocytes and mononuclear cells in the stroma.

The structure of the lymph nodes was almost completely replaced by a diffuse infiltration with mononuclear cells, only partially limited by the capsule, and extending into the surrounding tissue. Megakaryocytes were present in all the nodes, but were extremely numerous in one section in which they had actually engulfed mononuclear cells. The oxidase test showed a large number of oxidase-positive cells.

The bone marrow was very hyperplastic. The red cell series was crowded out by masses of cells of the mononuclear type. Very few cells of the granular series were present; megakaryocytes were numerous. Occasional mitoses were present. The type cell was one of moderate size, with nongranular, fairly abundant neutrophilic cytoplasm and a single more or less indented vesicular nucleus, closely resembling the blood monocyte.

The microscopic diagnosis was monocytic leukemia with leukemic infiltration of the spleen, liver, kidneys, lymph nodes and suprarenal glands.

Postmortem Bacteriologic Studies.—A culture from the lungs showed *Streptococcus viridans*, *Staphylococcus aureus* and *Pneumococcus*, type 18. A culture from the liver showed *Staphylococcus aureus* and *Streptococcus viridans*.

CASE 5.—Medical History.—A. C., a white high-school girl, aged 16 years, entered the hospital on Oct. 13, 1931, complaining of weakness, spots over the body, bleeding from the nose and soreness of the gums.

The patient had not been in good health for five months before admission, at which time she began to feel languid and did not care to take part in any activities, but preferred to remain quietly at home. The appetite became poor, and she complained of attacks of giddiness.

Three months before admission the patient noticed shortness of breath on moderate exertion. At this time her gums began to bleed after brushing the teeth, and she noticed for the first time discolored bluish spots under the skin sometimes occurring spontaneously but more frequently produced by slight trauma.

Two months prior to admission she had a sore throat. Examination by her physician revealed large tonsils, but owing to the tendency to bleed, operation was avoided. She frequently spat blood from her gums and from the posterior part of the pharynx. The tonsils remained enlarged and tender throughout the present illness.

Two weeks before admission blurring of vision occurred, and the patient had prolonged flowing of blood from the uterus, which persisted. The gums became more tender, the teeth loosened, and the breath was very offensive.

The family history was irrelevant. The past history revealed no illnesses except mumps and chickenpox early in childhood and a mild attack of pain in the joints,

probably rheumatic fever, four years prior to admission. The patient had always been extraordinarily well and strong until the present illness. Her dietary habits were good, and there were no idiosyncrasies or peculiarities in her diet. Her best weight was 154 pounds (69.9 Kg.), six months before admission. During the present illness she lost 13 pounds (5.9 Kg.).

Examination.—The patient was a young, tall, white, fairly well nourished and well developed American girl lying in bed in considerable discomfort with obvious lesions of the mouth.

The skin was pale, and many small petechial hemorrhages and larger ecchymoses were scattered over the neck, trunk and extremities. The mucous membranes were pale. Small hemorrhages were seen in the conjunctivae. The mucous membranes of the nose were injected, swollen and possibly hypertrophic. The epithelium of the lips and buccal cavity was swollen; the gums were spongy and hypertrophic. There were numerous hemorrhages into the mucous membranes of the mouth.

The pupils were equal and reacted normally to light and in accommodation. The retina was somewhat hyperemic, and several small hemorrhages were present in the right retina. The margins of the optic disks were somewhat indistinct.

The mouth was as described in the history, and the breath was very foul; several teeth were loose, and three teeth were badly decayed. There were several necrotic, gangrenous ulcers of the gums. The tonsils were considerably enlarged and injected.

The lungs were normal on physical examination, and roentgenograms revealed only moderate thickening of the roots of both lungs.

The heart was slightly enlarged to the left. A soft systolic murmur was present over the whole precordium, and a short diastolic murmur was heard at the apex. The blood pressure was 110 systolic and 64 diastolic.

The results of examination of the abdomen were not remarkable except that the liver and spleen were palpable about 2 cm. below the costal margins and were slightly tender.

Pelvic examination was not made because the patient was menstruating.

The neurologic findings were normal except for congestion of the optic nerve head.

The lymph nodes generally were slightly enlarged. Those in the cervical, left axilla and left inguinal regions were moderately enlarged, varying from 0.5 to 2 cm. in diameter.

Course.—The patient remained in the hospital eighteen days and grew progressively more ill. Numerous new ecchymoses appeared over the trunk, extremities and mucous membranes. Bleeding of the gums and frequent epistaxis occurred. Two transfusions of blood were given on October 20 and 23; they were of very transient benefit. The body temperature fluctuated between 98 and 103 F. The pulse rate varied from 120 to 160 beats per minute, and the respiratory rate, from 25 to 30 per minute. She became rapidly weaker and died on October 31. Permission for autopsy was denied.

Laboratory Examinations.—The results of studies on the blood are shown in table 3.

Urinalysis showed: specific gravity, 1.015; sugar, none; albumin, ++. The sediment contained several red blood corpuscles in each high power field. Occasional hyaline and granular casts were seen.

The stools were formed and dark. There was a strongly positive guaiac test for occult blood.

The sputum was negative for acid-fast bacilli. Numerous streptococci were present.

A smear from the ulcerated gums showed many fusiform bacilli and spirochetes.

The icteric index of the blood serum was 6 units. The bleeding time was much prolonged.

On admission roentgen examination of the chest revealed moderate thickening of the roots of both lungs, the pulmonary fields being otherwise clear.

CASE 6.—*Medical History*.—W. L., a white man, aged 32, married, a chauffeur, entered the hospital on Dec. 12, 1928. He stated that he was perfectly well until about ten weeks before admission, when it was noticed by his wife and friends that he was pale. His physician was consulted; he was given tonics and advised to stop work. No examination of the blood was made at this time.

Eight weeks before admission the patient noticed anorexia, and he felt tired. He stopped work but continued to feel distinctly under par. At this time he first noticed slight pain in the right side of the upper jaw which persisted and became more marked. The anorexia increased, and he occasionally vomited in the morning. He failed to sleep well and began to lose weight rapidly.

Two weeks before admission the patient complained to his physician of painful hemorrhoids which, however, did not bleed. On previous occasions during the past two years he had had some discomfort from mild bleeding hemorrhoids. Pallor was becoming more marked, and he was definitely short of breath on exertion.

One week before admission marked sweating occurred, and the patient experienced several chills. The pain in the right side of the upper jaw became more annoying, and three days before admission a dental bridge was removed. The gums became markedly swollen and tender. He had lost 15 pounds (6.8 Kg.) during the last few weeks.

The only disease which the patient remembered having was typhoid fever at the age of 10 years. He stated that he had always been irregular in his sleeping and eating habits. No other significant dietary history was obtained. During the past two years he had worked considerably with ethyl gasoline and noticed that the gasoline fumes frequently made him feel nauseated. The family history was of no significance, except that his mother had died many years before of tuberculosis.

Examination.—The patient was a pale, well developed and moderately well nourished young man lying in bed in obvious discomfort owing to swelling and soreness of the face on the right side.

The skin was sallow, and a few small, fresh hemorrhages were present over the trunk.

The mouth was the site of chief discomfort. The teeth were poorly kept and contained a few cavities. The gums were greatly swollen, and in the region of the right upper molars there was a large, tender, sloughing, ulcerated area. The swelling extended to the whole right side of the face and was of distinctly higher temperature than the other side. The mucous membranes of the pharynx were swollen and injected; the tonsils were moderately enlarged.

The heart was not enlarged, and no abnormal sounds were heard, but the rate was rapid, 110 per minute. The blood pressure was 120 systolic and 75 diastolic. The lungs were normal to percussion and auscultation.

The liver and spleen were palpable 1 cm. below the costal margin and were slightly tender.

There was moderate general enlargement of the lymph nodes.

The extremities were normal. Neurologic examination revealed no abnormal findings.

Course.—The anemia, which was severe on admission, became somewhat more intense. The lesions in the mouth progressed. The body temperature varied from 98.4 to 104 F. Blood cultures were positive for *Staphylococcus albus*, *Streptococcus haemolyticus* and *Bacillus coli-communis*. The pulse rate fluctuated between 110 and 120, and the respiratory rate, from 25 to 40 per minute. The patient gradually became more dyspneic and died on December 23, eleven days after admission. Permission for autopsy was not obtained.

Laboratory Examinations.—The results of studies on the blood are shown in table 3.

The urine was negative for sugar. Albumin was constantly present in moderate amounts. White blood cells and hyaline and granular casts were present in increased numbers in the sediment.

The blood sugar was 113 mg. per hundred cubic centimeters. The nonprotein nitrogen of the blood was 37 mg.

Cultures from the gangrenous gums showed *Streptococcus haemolyticus*.

Roentgenograms of the teeth showed no abscesses.

ACUTE MYELOGENOUS LEUKEMIA

CASE 7.—Medical History.—P. G., a white American youth, aged 17, entered the hospital with the complaint of bleeding from the mouth following extraction of a tooth.

The patient was in a critical condition and semicomatose on admission. No relatives or associates could give a detailed history. He was, so far as could be learned, perfectly well until one week before admission, at which time a tooth was extracted. There was profuse bleeding, said to be about a liter, at the time of extraction, and moderate bleeding continued throughout the week until admission. No information concerning the past history or family history could be obtained.

Examination.—The patient was a fairly well developed and fairly well nourished young man, semicomatose, moderately dyspneic and very pale. There were numerous very small petechial hemorrhages scattered over the trunk and extremities. The mucous membranes were very pale and were the sites of small hemorrhages. There was oozing of blood from a tooth cavity and around the edges of the remaining teeth, but there was no ulceration, gangrene or diffuse swelling of the mucous membranes. There were several rather extensive hemorrhages into the mucous membranes of the lips.

A complete physical examination was not done owing to the patient's critical state. The lymph nodes in the neck, axillae and inguinal regions were not enlarged. The heart was slightly enlarged, and there was a blowing systolic murmur over the whole precordium. The pulse rate was 120 per minute. The lungs were normal. The edge of the liver could not be felt, and the edge of the spleen was palpable only on deep inspiration. No other abnormalities were noted. On one examination the urine showed no sugar, a trace of albumin and no acetone or diacetic acid. The urinary sediment contained a few white blood cells, red blood cells and occasional hyaline and granular casts. The results of the study of the blood are shown in table 3.

Course.—Soon after admission to the hospital a transfusion of 400 cc. of citrated blood was given. The next day the patient was obviously in a more critical state. The body temperature was 102 F.; the pulse rate rose to 160 beats per minute, and the respiratory rate to 45 per minute; there was marked dyspnea. In spite of supportive treatment, the patient died about thirty-six hours after admission.

Postmortem Examination.—Gross Appearance: No lymph nodes were palpable except a few in the inguinal region, measuring 1 cm. in diameter. The skin and mouth were as described in the physical examination recorded. The peritoneal serosa was smooth and without exudate. The domes of the diaphragm rose to the fifth rib on the right and to the fifth interspace on the left.

The liver weighed 2,030 Gm., and its edge was 2 cm. below the right costal margin. Its capsule was thin and the surface smooth. Section of the liver showed a pale, grayish mottling on a light brown background. The consistence was soft. The gallbladder was normal.

The spleen weighed 240 Gm. The capsule was thin and smooth. A section through the organ revealed a soft purplish-gray surface with numerous round, gray areas from 2 to 3 cm. in diameter scattered throughout. The cut surface scraped away with ease.

The pancreas and suprarenal glands were normal.

The kidneys weighed 380 Gm. The capsules stripped with ease, leaving smooth surfaces. The cortex was uniform and measured 6 cm. in width. The renal tissue was pale and somewhat soft, but otherwise normal.

The gastro-intestinal tract, genital organs, abdominal vessels and urinary bladder were normal.

The surfaces of the pericardial cavity were smooth. About 75 cc. of clear amber-colored fluid was present.

The heart weighed 440 Gm. There were marked dilatation and slight hypertrophy. Beneath the visceral pericardium were numerous red areas from 1 to 2 cm. in diameter. The heart muscle was soft and pale and showed no areas of scarring. There were numerous small endocardial hemorrhages. The valves and the coronary vessels were normal.

The pleural cavities were normal.

Both lungs were soft and light in color. No areas of consolidation or of scarring were found.

Sections of the bone marrow were removed from the sternum, vertebrae and femur. The marrow was soft and grayish pink and appeared to be hyperplastic.

Microscopic Appearance: The blood vessels of the heart and lungs were filled with large white blood cells which contained large round nuclei with rather coarse chromatin masses. The cytoplasm of these cells was small or moderate in amount, blue staining and granular. Occasional cells were present with blue granules. No other abnormalities were noted in these organs.

The sinuses of the spleen were filled with cells. Many areas were present in which fibrin had been deposited, and hyaline changes had occurred. The architecture of the spleen was partially obliterated by the cellular hyperplasia.

There was extensive central necrosis of the liver, with some extravasation of red blood corpuscles. The sinusoids were distended and filled with cells similar to those described in the vessels of the heart and lungs. There was slight infiltration of the periportal connective tissue with these cells.

The pancreas was normal.

The renal tubules were distended. The blood vessels were the same as those in the heart.

The suprarenal glands showed slight infiltration with the type cells as described in the blood vessels.

The sinuses of the lymph nodes were filled with the type cells. The architecture was somewhat distorted.

In the bone marrow there was marked hyperplasia, the large uninuclear cells predominating. These cells appeared to be myeloblasts and early myelocytes. The areas of formation of red blood corpuscles were greatly reduced in number.

The microscopic diagnosis was myelogenous leukemia.

Postmortem Cultures.—Cultures of the heart's blood and bone marrow showed no growth.

ACUTE LYMPHATIC LEUKEMIA (LEUKOSARCOMA)

CASE 8.—*Medical History.*—C. T., a white American schoolboy, aged 10 years, entered the hospital on Jan. 28, 1931, because of cough, pain in the abdomen and pallor.

The past history was not remarkable except that two years before admission the patient had whooping cough, measles and chickenpox with uneventful recoveries. Aside from occasional colds he had no other illnesses. The family history was not significant. The patient had received an adequate diet, and there was no history of abnormalities in his likes or dislikes for special articles of food.

Six months before admission the school physician had reported disease of the tonsils and adenoids, but no operation or other treatment was advised or undertaken.

Six weeks before admission the present illness began with a persistent cough. The patient had no fever and was not kept in bed, but he did complain of some pain between the shoulders and in the upper part of his abdomen.

The family physician found no abnormalities. Soon afterward his mother noticed that the child was becoming pale, was breathless on moderate exertion and was taking less food than usual. He was given cough medicine, which brought about some improvement, but his appetite remained poor, and soon the cough became more troublesome.

Three weeks before admission a moderate nosebleed occurred. The family physician again examined the patient, but found nothing abnormal. No studies of the blood were made at this time.

One week before admission all the symptoms became more severe, and the patient's physician discovered an enlargement of the spleen. The left eye became discolored as the result of a spontaneous hemorrhage. The urine was found to be normal.

After a few days a consultant made a diagnosis of acute leukemia, and the patient was referred to the hospital.

He had no bleeding or ulceration and no pain in his mouth or pharynx.

Examination.—The patient was quite emaciated, sitting propped up in bed, with obvious discomfort. The skin was pale and contained only two moderate-sized petechial hemorrhages. There were large subconjunctival hemorrhages in each eye and what appeared to be a hemorrhage into the deeper structures behind the eyeball on the left side. Examination of the fundi showed numerous small hemorrhagic areas with grayish centers, the type of lesion so often seen in leukemia. There were a few crusts of blood in the nose but no discharge. The lips were slightly cyanotic. The mucous membranes of the mouth and pharynx were in good condition, except for a few small petechial hemorrhages on the soft palate. There was no ulceration or swelling of the gums. The tonsils were enlarged and cryptic, but presented no evidence of acute infection.

There was rather marked general enlargement of the lymph nodes. In the neck these nodes were firm and discrete, about 0.5 cm. in diameter. In each axilla there were masses of lymph nodes some of which were from 2 to 5 cm. in diameter,

firm, smooth and not tender. Both epitrochlear lymph nodes were easily palpable and were about 1 cm. in diameter. There were enlarged inguinal nodes, and a mass of lymph nodes could be felt in the pelvis just under the pubic ramis.

The chest was rather asymmetrical, with a large anteroposterior diameter and some fulness in the upper part of the left side. The percussion dulness over the anterior mediastinum was of interest. In the second interspace the substernal dulness was 9 cm. in width. The left border of cardiac dulness was 11.5 cm. to the left of the midsternal line in the sixth intercostal space. No murmurs were heard. The pulse was regular, rapid (130 per minute) and of low volume. The blood pressure was 90 systolic and 60 diastolic. The pulmonary fields showed slight impairment of the percussion note over the upper lobes on each side, and in this area there was high-pitched tubular breathing together with accentuated whispered breath sounds. There were a few moist râles in the bases of both lungs.

The abdomen was full. The edge of the liver was smooth and slightly tender 7 cm. below the right costal margin in the nipple line. The spleen extended 12.5 cm. below the costal margin in the nipple line.

Examination of other parts of the body showed them to be normal, except that the deep reflexes of the extremities were not obtained, possibly because of the semicomatose condition of the patient.

Laboratory Examinations.—The blood was remarkable (table 3). There were 1,110,000 white blood cells per cubic millimeter, one of the highest white blood cell counts on record. The Wassermann reaction of the blood was negative.

The urine was yellow and neutral to litmus; it contained no sugar, acetone or diacetic acid; the specific gravity was 1.025. There was a trace of albumin. The sediment contained a few red and white blood cells.

Course.—Soon after admission to the hospital the patient was given a transfusion intravenously of 300 cc. of normal citrated blood. He was also given intravenously, purely as a trial, two small doses of pentnucleotide. The body temperature varied from normal to 100.8 F., and the pulse rate and respiratory rate were constantly elevated from 125 to 140 per minute and from 32 to 55 per minute, respectively. The patient lapsed further into coma and died three days after admission.

Postmortem Examination.—Gross Appearance: The external appearance was as described in the clinical history.

The surfaces of the peritoneal cavity were smooth. The domes of the diaphragm rose to the sixth rib on the right side and to the seventh rib on the left. The edge of the liver extended 11.5 cm. below the xiphoid process and 10 cm. below the right costal margin in the midclavicular line. The appendix was normal. The mesenteric lymph nodes were enlarged, from 0.5 to 1.5 cm. in diameter, and were firm in consistence.

The right pleural cavity contained about 1,000 cc. of amber-colored fluid. The anterior mediastinum was obliterated by a tumor extending from the sternal notch to the xiphoid process. This mass was adherent to the sternum for a distance of 3 cm. on either side of the midline. The posterior limits of the mass were the pericardium, which it completely covered. The tumor tissue had invaded the medial surfaces of both lungs, particularly on the right side. The middle and lower lobes of the right lung were collapsed and almost completely invaded by tumor tissue. This tissue was hard and yellowish white. The thymus gland could not be identified, but presumably was completely destroyed by the tumor.

The surfaces lining the pericardial cavity were smooth but were encased in the mass of tissue previously described. About 50 cc. of clear, amber fluid was present.

The heart and lungs were found to be as previously described. There were in addition underneath the visceral pericardium a few small, round, purple areas 1 or 2 mm. in diameter.

The spleen weighed 520 Gm. The capsule was thin and smooth. The cut surface was grayish purple and soft; the tissue could be scraped away with ease.

The liver weighed 1,380 Gm. The capsule was thin and the surface contour smooth. The liver was pale brown and soft. The gallbladder was normal.

The gastro-intestinal tract, pancreas, kidneys, suprarenal glands, urinary bladder, genital organs and aorta were normal on gross inspection.

In the femur the bone marrow was soft, cellular and a purple-red. The bone marrow of the vertebrae was dark red.

Microscopic Appearance: The lungs showed extensive infiltration with tumor cells. The type cell of the tumor was a cell which could be described as a small or intermediate-sized round cell presumably of the lymphoid strain. The nuclei were quite dark with chromatin, and the cytoplasm was small in amount. Mitotic figures were seen frequently.

The structure of the spleen and lymph nodes was masked by diffuse infiltration with the type cell. Mitotic figures were present in increased numbers. Occasional eosinophilic leukocytes were present.

The sinusoids of the liver were filled with the type cells. The periportal areas were infiltrated with the cells.

Normal bone marrow had been replaced by very hyperplastic tissue, chiefly composed of the round mononuclear cells previously described.

The other viscera showed the vessels and perivascular areas to be heavily infiltrated with tumor cells.

The microscopic diagnosis was lymphatic leukemia with mediastinal tumor (leukosarcoma).

Postmortem Cultures.—Cultures of the spleen and pleural fluid showed no growth.

COMMENT

In addition to the six cases of acute monocytic leukemia, the blood smears in three additional cases have been observed. One of these cases has been reported by Clough.⁶ Another is to be reported subsequently.⁸ The blood smears in each of these nine cases were very similar and in each the clinical history and physical examination revealed certain common characteristics.

Lesions of the Mucous Membranes as Aid in Differentiation of the Acute Leukemias.—It is my opinion that the clinical picture of diffuse, marked swelling of the mucous membranes, particularly of the gingivae usually with ulceration and necrosis, is characteristic of acute monocytic leukemia and is usually absent in acute leukemia of the myelogenous or lymphatic varieties. In association with these lesions of the mucous

8. Unpublished case in a Chinese to be reported from the Cheeloo University Medical School, Tsinan, Shantung, China.

membranes there occurs, usually, what appears to be a diffuse cellulitis about the lesions, causing swelling and pain with signs of acute inflammation extending into the deeper tissues of the face. Because of these presenting symptoms, all of the patients suffering from acute monocytic leukemia whose cases are reported in this communication consulted their dentists early in the course of their illness. It is true that patients with acute lymphatic leukemia and acute myelogenous leukemia frequently have symptoms referable to the mouth and other mucous membranes, but in my experience these lesions have been of a different sort and have been limited to hemorrhages and slight infection, and as a rule have not been characterized by diffuse swelling with ulceration and necrosis.

These differences in the clinical picture have not been appreciated heretofore. The impression conveyed in textbooks and in the papers on acute leukemia is that the symptoms are similar for all types, although all patients do not exhibit the same symptoms.

Of the twenty-three cases referred to by Clough⁶ as probably authentic cases of monocytic leukemia, twenty-two have been reviewed in the present study with particular reference to the presence of lesions of the mouth. The report of the case by Sega and Brustolon⁹ was not available for study. Of these twenty-two patients, eighteen had symptoms of marked stomatitis or pharyngitis with swelling of the gums, and in the majority ulceration, alveolar abscesses or sinus abscesses were present. Of the four remaining patients, one (Rosenthal¹⁰) had swelling of the neck but no reported lesions of the mucous membranes; a second patient (Ugriumow¹¹) probably did not have acute monocytic leukemia but lymphatic leukemia with a mediastinal tumor (leukosarcoma); the third and fourth cases (Swirschewskaja¹² and Lawrence, Josey and Young¹³) were of the subacute or chronic variety and therefore were not applicable to this study.

Eight additional cases, some of which were not accepted by Clough and others and were published subsequent to his study, have also been reviewed. The three cases reported by Ewald, Frehse and Hennig¹⁴

9. Sega, A., and Brustolon, A.: *Leucemia monocitica o reticulo-endoteliosi leucemica?* *Haematologica*, I. Arch. **10**:471, 1929.

10. Rosenthal, N.: *Some Atypical Cases of Leukemia*, *M. Clin. North America* **4**:1607, 1921.

11. Ugriumow, B.: *Ein Fall von akuter Retikulo-Endotheliose*, *Centralbl. f. allg. Path. u. path. Anat.* **42**:103, 1928.

12. Swirschewskaja, B.: *Ueber leukämische Retikuloendotheliose*, *Virchows Arch. f. path. Anat.* **267**:456, 1928.

13. Lawrence, J. S.; Josey, A. I., and Young, M.W.: *Three Cases of Monocytic Leukemia*, *Folia haemat.* **44**:332, 1931.

14. Ewald, Frehse and Hennig: *Akute Monocyten- und Stammzellenleukämien*, *Deutsches Arch. f. klin. Med.* **138**:353, 1922.

in 1922, one additional case by Bingel¹⁵ in 1916, one case by Dias¹⁶ in 1930, one by Hittmair¹⁷ in 1930 and two cases by Asselstine¹⁸ in 1932 showed lesions of the mouth similar to those in the eighteen cases of acute monocytic leukemia. Other recent reports of cases by Muenzer,¹⁹ Reich,²⁰ Lazzarini²¹ and Invernizzi²² were not available for study.

This analysis of the literature shows a striking uniformity in the lesions of the mucous membranes encountered in acute monocytic leukemia and is in agreement with my observations on this disease (table 4).

Other Physical Signs as Aids in Differentiation of the Acute Leukemias.—Not only do the symptoms and signs referable to the mucous membranes serve as aids in the differentiation of the acute leukemias, but there also exist other physical signs which, at least in adult patients, serve a similar purpose. It is usually true that the spleen, although somewhat enlarged, is not palpable in acute myelogenous leukemia, whereas in acute lymphatic leukemia the spleen is larger and is, almost without exception, palpable 2 or 3 cm. or even more below the costal margin. The spleen in acute monocytic leukemia, according to Clough, was palpable in sixteen of the twenty-four cases reviewed. In five of the six cases reported in the paper the spleen was easily palpable from 1 to 4 cm. below the costal margin. The weight of the spleen at autopsy in the first four cases reported in this communication was 1,065, 606, 360 and 900 Gm., respectively.

The size of the lymph nodes is also an aid in the differentiation of acute leukemia. It is my experience that usually, in fact almost invariably, there is a distinct general enlargement of the lymph nodes in acute lymphatic leukemia. This enlargement often is by no means as marked as that usually found in chronic lymphatic leukemia. The lymph nodes, particularly those in the neck, may be slightly or moderately enlarged in acute monocytic leukemia, but general enlargement to the extent found in acute lymphatic leukemia usually is not seen. It is even

15. Bingel: Monozytenleukämie? Deutsche med. Wchnschr. **42**:1503, 1916.

16. Dias, A.: Monocytose aiguë: Leucémie monocyttaire, Rev. sud.-am. de méd. et de chir. **1**:41, 1930.

17. Hittmair, A.: Akute Myelose mit monozytoiden Zellformen, Folia hæmat. **42**:271, 1930.

18. Asselstine, S. M.: Acute Monocytic and Lymphatic Leukemia, Canad. M. A. J. **26**:174, 1932.

19. Muenzer, J.: Monocytic Leukemia in Children, Polska gaz. lek. **8**:796, 1929.

20. Reich, C.: Monocytoid Myeloblastic Leukemia, New York State J. Med. **32**:1193, 1932.

21. Lazzarini, L.: Reticulo-Endotheliosis with Acute Leukemia, Osp. maggiore **18**:33, 1930.

22. Invernizzi, G.: Acute Monocytic Leukemia, Morgagni **73**:2329, 1931.

more uncommon to find generalized enlargement of the lymph nodes in acute myelogenous leukemia, and if any such enlargement is found it is slight (table 4).

TABLE 4.—*Clinical and Histologic Differentiation of the Three Main Types of Acute Leukemia*

	Acute Myelogenous Leukemia	Acute Lymphatic Leukemia	Acute Monocytic Leukemia	
Spleen.....	Usually not palpable	Almost invariably significantly enlarged	Palpable in about 70 per cent of cases	
Lymph nodes.....	Usually slight or no enlargement	General enlargement of moderate or marked degree	Moderate in neck, but other lymph nodes very slightly en- larged, if at all	
Liver.....	Usually palpable	Usually palpable from 1 to 4 cm. below costal margin	Usually palpable from 1 to 4 cm. below cos- tal margin	
Mucous membranes, particularly of mouth and pharynx	Petechiae, bleeding; often slight swelling of gingivae but rarely ulceration	Petechiae, bleeding; rarely ulceration	Petechiae, bleeding; usually marked, dif- fuse swelling of gingivae or pharynx with ulceration; often cellulitis with swelling and tenderness of face; marked fetor oris	
Histologic distinctions of type cells in blood and tissues	Oxidase reaction	From few to many oxidase-positive cells, with from few to many coarse granules	All lymphoid cells oxidase-negative	All monocytes positive or all negative, or some positive and others negative; pos- itive cells contain relatively few fine granules
	Other charac- teristics	Dominant cells myelo- cytes "A" (Sabin) and myeloblasts; nuclei round or oval, usually with several nucleoli; cytoplasm deeply basophilic; myelocytes "B" (Sabin) present; Auer's bodies fre- quently present in few cells	Dominant cells lym- phoblasts and young lymphocytes; nuclei round, oval or slightly indented, with few nucleoli usually pres- ent; relatively small amount of deeply basophilic, hyaline cytoplasm; mature lymphocytes present in fair number; occa- sional myelocytes "C" (Sabin) and meta- myelocytes present	Dominant cells mono- blasts and premono- cytes; nuclei usually elongated and folded, deeply indented or otherwise irregular in contour; nucleoli rarely present; cyto- plasm relatively abundant, usually not deeply basophilic and not hyaline but slightly basophilic and "ground glass- like"; Auer's bodies may be present in few cells; mature monocytes present in significant and vary- ing numbers; myelo- cytes "C" and meta- myelocytes often present in small numbers

Thus there are certain characteristic features in the history, symp-
tomatology and physical signs which aid materially in the differentiation
of the three main types of acute leukemia. These characteristics, in the

absence of a clearcut blood picture or of histologic studies on the tissues, are of value in establishing the diagnosis.

Hematologic Differentiation of the Acute Leukemias.—The cytologic aspects of the blood in acute leukemia are of great interest. This phase of the subject has been frequently discussed and well presented in many papers on the subject and need not be reviewed in detail in this communication. The definitive structural elements in the blood are readily classified, but when immature cells are found they frequently give rise to confusion, depending on the degree of immaturity. This confusion is enhanced in acute leukemia by a singular fact which does not occur in any other disease. The great majority, often more than 85 per cent, of the white blood cells in a given case of acute leukemia are of a uniformly immature type, usually in the myeloblast, monoblast or lymphoblast stage of development. Intermediate stages in the development of the type cell are therefore few and frequently do not permit safe deductions as to the type of cell by observation of intermediate phases in maturation. This difficulty is further accentuated by the fact that owing to the greatly disorganized hematopoietic system immature cells of strains other than that of the type cell may be present in small numbers in the blood. Hence one must rely on the finer cytologic characteristics of lymphoblasts, monoblasts and myeloblasts, and as all of these are sister cells derived from the same more primitive mesenchyme cells, their accurate differentiation is not always possible.

Sabin,²³ Simpson²⁴ and others have, in recent years, rediscovered a valuable method for the histologic study of blood and tissue cells. This so-called supravital technic is of particular value in the differentiation of the monocytic strain of cells and aids materially in the recognition of early myelocytes and their immediate precursors the myeloblasts. In certain cases it is only by a combination of all the available methods of study that an acceptable opinion concerning the type cell may be established. Certain other distinctly rare cases defy classification. The latter group, in the absence of other aids in the diagnosis, is usually regarded as stem cell leukemia or acute leukemia of undetermined type.

There are, however, commonly present certain distinctions in the cell types which have been illustrated in the accompanying drawings (fig. 1) of cells from the blood of patients with the three types of acute leukemia under discussion. The group of five cells illustrated in the upper left hand corner of the plate are from the blood of the patient

23. Sabin, F. R.: Studies on Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

24. Simpson, M. E.: Vital Staining of Human Blood with Special Reference to the Separation of the Monocytes, Univ. California Pub. on Anat. **1**:1, 1921.

EXPLANATION OF FIGURE 1

Fig. 1.—Cells from the blood of patients suffering from acute leukemia. The plate is divided into four sections: upper left, upper right, middle and lower. In these sections are colored camera lucida drawings of cells from the blood of four patients in the cases reported in this communication. The cells were stained by Wright's method and magnified 1,400 \times .

1. In the upper left hand corner are drawings of five white blood cells from the blood of the patient in case 7; the case was one of acute myelogenous or myeloblastic leukemia. The cells are myeloblasts and very early myelocytes (myelocytes "A" of Sabin).

2. The four white blood cells drawn in the upper right hand corner of the plate represent the dominant cells in the blood in case 2, one of acute monocytic leukemia. The cells are monocytes and premonocytes, possessing the characteristic nuclei and cytoplasm of such cells.

3. The nine cells represented in the middle section, right and left, are typical of those in the blood in case 1. The smallest of the cells is a small lymphocyte drawn for comparison. The other cells are monocytes in various stages of development. The large cell on the extreme left contains in its cytoplasm structures resembling Auer's bodies. The deeply basophilic cell on the extreme right is difficult to classify, but probably is an abnormal type of the monocytic strain of cells. The large cell just above the deeply basophilic cell is a young monocyte or premonocyte. The other cells represent later stages in maturation of monocytes.

4. The eight cells shown in the bottom section of the plate were found in the blood in case 8, one of acute lymphatic leukemia. The largest of these cells is shown in the process of mitosis. The smallest cell is an adult small lymphocyte. A typical polymorphonuclear neutrophilic leukocyte was drawn for comparison. The remaining five cells represent immature lymphocytes.

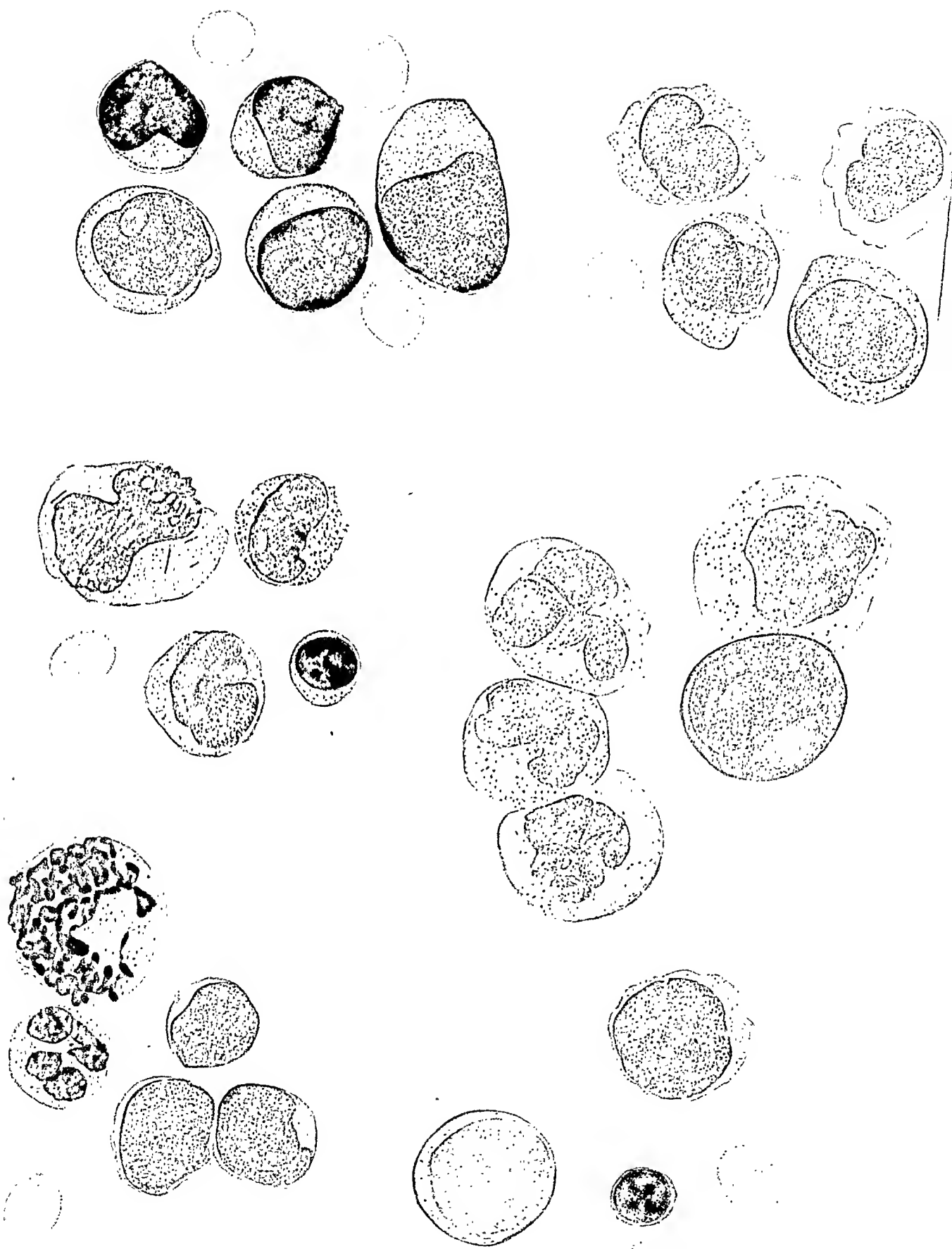


FIGURE 1

in case 7 (acute myelogenous leukemia) and illustrate the essential characteristics of myeloblasts. The nuclei are large, round, oval or slightly indented and contain several nucleoli. The cytoplasm is deeply basophilic and of uniform character. The four cells in the upper right hand corner belong to the monocyte series and were from the blood of the patient in case 2 reported in this paper. The five cells in the right middle section of the plate and the four in the left middle section were from the blood of the patient in case 1 (acute monocytic leukemia). All of them except the small lymphocyte in the left middle section represent various forms of monocytes, premonocytes and monoblasts. The nuclei for the most part tend to have a complicated shape and possess very few nucleoli. The cytoplasm is relatively abundant, is generally less basophilic and contains many dustlike granules. One of the cells contains several elongated reddish structures (Auer's bodies) in the cytoplasm. The large deeply basophilic cell on the right is presumably a very young monoblast or possibly an atypical premonocyte. The eight cells occupying the bottom one third of the plate were from the blood of the patient in case 8 (acute lymphatic leukemia). One of these cells is a definitive young lymphocyte, another a polymorphonuclear neutrophil and another a large lymphoid cell in the process of mitotic division. The other five cells are immature lymphocytes; they have large nuclei with diffuse chromatin distribution and a relatively small amount of hyaline, moderately basophilic cytoplasm.

Histologic Differentiation of the Acute Leukemias.—Just as the clinical and hematologic differentiation of the acute leukemias is often difficult and doubtless frequently incorrectly made, so it is also with the pathologic differentiation. The chief criterion on which the pathologist relies is the oxidase reaction of the tissues. If the cells infiltrating the liver, kidney and other tissues are oxidase-positive and if the architecture of the blood-forming organs is disorganized and shows indiscriminate hyperplasia of uniformly immature cells, the diagnosis of myelogenous leukemia is made. On the other hand, if such a state exists, but without a positive oxidase reaction, the diagnosis of lymphatic leukemia or of lymphoblastoma is in order.

With the discovery of a third type of leukemia—monocytic—the pathologic diagnosis becomes more difficult, because in this type the oxidase reaction of the tissues or of the blood cells may be either positive or negative, and hence the chief point for the differential diagnosis is lost. There are, however, certain characteristics of the histology which are of great importance, which are little appreciated and which usually are distinctive. Although often it is extremely difficult or impossible in good paraffin sections to distinguish lymphoblasts from myeloblasts, this is not true of monocytes and their precursors. The

latter cells, when observed by means of the oil immersion lens in the blood or in their sites of formation in the tissues, have certain characteristics distinguishing them from myeloblasts or lymphoblasts. The nuclei, even of premonocytes and of monoblasts, are usually of irregular shape, often in the form of an irregular crescent or a broad elongated nucleus bent on itself. Frequently the nucleus is bent on itself several times, giving the impression of lobulation, although distinct separation of the lobules is rarely demonstrable in contrast to the characteristic nucleus of the polymorphonuclear granulocyte. There exist also many young cells of the monocyte series which have simple round, oval or slightly indented nuclei, but these cells exist as close companions of the cells with the more complicated nuclei as described. Furthermore, other characteristics distinguish the monocytic cells from the early lymphoid and myeloid elements. The nuclei of the monocytic series of cells rarely have demonstrable nucleoli, whereas these structures are very common in lymphoblasts and myeloblasts. The cytoplasm of premonocytes and monoblasts is, as a rule, more abundant and much less basophilic than that of either lymphoblasts or myeloblasts and frequently is so faint, with hematoxylin and eosin or with eosin-methylthionine chloride, U. S. P. (methylene blue) stains, that the border of the cell is barely recognizable. This appearance is in contrast to the moderate or very deep basophilia of early lymphoid and myeloid cells.

There has been much controversy concerning the existence or absence of granules in monocytes giving a positive reaction to oxidase or peroxidase staining. Certainly it is true that the great majority of the normal monocytes in human blood when stained with the copper sulphate-benzidine-peroxide-safranin method of Sato and Sekaya do possess blue granules, similar to but not identical with those in neutrophilic myelocytes. This is in contrast to the total absence of such granules in all the cells of the lymphoid series. It appears also to be true that a few perfectly definite monocytes in the blood of normal persons and frequently many of the early monocytes in pathologic states may possess no such granules. When present the oxidase or peroxidase granules in monocytes are smaller and fewer than those encountered in myelocytes, and this characteristic at times is useful as an aid for differentiation.

The essential destruction of the normal architecture of the hematopoietic organs and its replacement by a disordered hyperplasia of immature blood cells is then a characteristic of all types of leukemia. Careful studies of the oxidase reaction and of the character of the type cells dominating the picture is essential for histologic differentiation of the three main types of acute leukemia.

Origin of the Monocyte.—No subject in hematologic literature has been the source of more controversies than this much disputed question. There exist no less than nineteen separate views on the origin of the monocyte (fig. 2). Fibroblasts, primitive undifferentiated cells, lymphoid cells, the endothelium of the blood vessels, reticulo-endothelial cells, myeloblasts and various miscellaneous cells have all been claimed to be the mother cells of monocytes. Many of these views have been obtained from the study of the diseased tissues. It is fair to say that in normal man the development of monocytes in the blood-forming tissues has never been demonstrated. In animals in no organs or tissues, other than in certain lymph nodes, chiefly the peripheral group, can one find constantly monocytes in all stages of development.²⁵ In these lymph nodes they have been shown to arise from primitive undiffer-

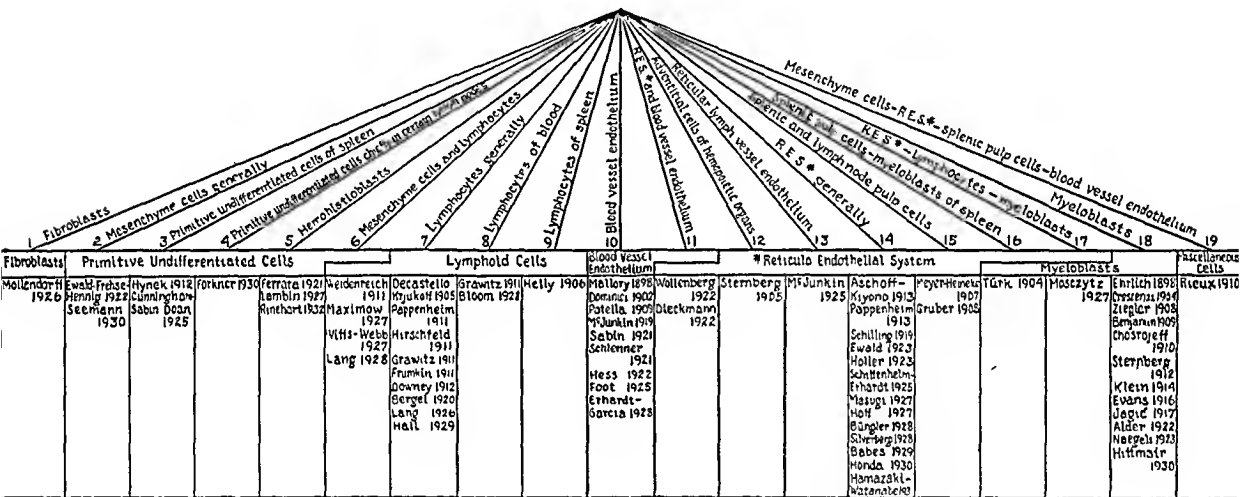


Fig. 2.—Theories of the origin of monocytes.

entiated cells going through the stages of monoblasts and premonocytes to definitive monocytes.²⁵

It was hoped that a study of these cases of monocytic leukemia would throw some light on the origin of the monocyte in man. However, since all the hematopoietic tissues, as in the other types of acute leukemia, were crowded with the type cells, no conclusions as to origin were possible.

SUMMARY AND CONCLUSIONS

Eight cases of acute leukemia are presented, six of acute monocytic leukemia and one each of the acute myelogenous and acute lymphatic types.

25. Forkner, C. E.: Material from Lymph Nodes: IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte; Supravital Studies, J. Exper. Med. **49**:323, 1929; The Origin of Monocytes in Certain Lymph Nodes and Their Genetic Relation to Other Connective Tissue Cells, *ibid.* **52**:385, 1930.

The three main types of acute leukemia, contrary to accepted belief, have certain distinctive clinical features.

Attention is directed particularly to the symptoms and signs referable to the upper alimentary and respiratory tracts and those associated with hyperplasia of the hematopoietic tissues.

Certain histologic differences exist in the blood and tissue cells which are diagnostic of the various kinds of acute leukemia.

This study has been confined mainly to acute leukemia in adult patients and, therefore, in some respects may not be applicable to this disease as it occurs in young children.

These studies were made in Dr. George R. Minot's laboratory. Dr. Frederick Parker, Jr., aided in the pathologic study.

CARDIAC OUTPUT

ITS RELATED FUNCTIONS IN A CASE OF COARCTATION OF THE AORTA

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AND

J. P. FERRIGAN, JR., A.B.

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Coarctation of the aorta presents several features of interest concerning the hemodynamics and regulation of the circulation, for it presents a condition in which the brain and carotid sinus, the chief sites of any central regulatory functions, are subjected to an arterial hypertension while the lower extremities and viscera are supplied with blood at a lower pressure. The cardiac output has not hitherto been studied in cases of coarctation. Because of the relative infrequency with which the condition is recognized in young persons before the advent of secondary complications, and because of the interesting theoretical considerations involved, the results obtained in a single person have been considered worthy of a report.

REPORT OF A CASE

Clinical History.—The subject of our study, J. P. F., Jr., was a medical student, 25 years of age. His family and past history were entirely irrelevant. Except for diphtheria, measles, chickenpox and occasional colds, his health had always been good.

In the course of a routine physical examination in January, 1924, he was told that he had "chronic endocarditis." At that time he was pursuing an active life, engaging in athletics and had suffered no discomfort. The examination revealed a systolic blood pressure of about 185 mm. but the test was taken in only one arm. This diagnosis was confirmed by several physicians. The patient was put on a low protein and low salt diet and was ordered to have complete quiet and rest.

At the end of two months, this regimen was relaxed. The diet was gradually returned to normal and more activity was permitted in the course of the next two and one half years, during which time he was constantly under the observation of a physician. There was no apparent change in his condition, except a slight decrease in the systolic blood pressure as taken in either the right or the left arm.

In October, 1931, he entered medical school. In the course of a routine physical examination a roentgenogram showed scalloping of the inferior borders of the ribs; and a diagnosis of coarctation of the aorta was made by Dr. Charles C. Waters.

Subsequent examinations by Dr. John T. King, Jr., and Prof. Warfield T. Longcope confirmed this diagnosis and showed the presence of the other diagnostic

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signs of the adult type of coarctation,¹ such as higher blood pressure in the arms than in the legs, bilateral pulsations in the interscapular region and systolic murmur along the vertebral borders of the scapulae. There were also signs of aortic insufficiency, indicative of the presence of some defect of the aortic valves which occurs commonly in cases of coarctation.¹

Subjectively the patient manifested no signs of incompetence of the cardiovascular system. He engaged in severe exercise (tennis and swimming) with no discomfort, and was otherwise free from symptoms (the claudication of the lower extremities, abdominal distress) encountered in this condition. Analysis of the urine showed it to be normal; the hemoglobin content was 120 per cent, with an erythrocyte count of 5,600,000.

Experimental Findings.—The cardiac output was determined by the acetylene method on two separate occasions. Duplicate determinations were made in the basal resting condition as prescribed in detail elsewhere.² The cardiac output was 4.8 and 5 liters, an average value of 4.9 liters, with an average arteriovenous oxygen difference of 61 cc. per liter. Although this arteriovenous difference is within the range of normal values found in persons of the age of the patient, the cardiac output was higher than is normal, owing to the elevated oxygen consumption. This was reflected in a high cardiac index. The patient's height was 180 cm. and his weight was 77 Kg. His surface area was 1.96 square meters as calculated by DuBois' formula.³ Therefore, his cardiac index was 2.5 liters per square meter of body surface, which is approximately 15 per cent above normal.

The elevated cardiac index observed in our subject in the presence of a normal arteriovenous oxygen difference is similar to that observed in hyperthyroidism and is a concomitant of the elevated oxygen consumption.² The increased cardiac output might thus be looked on as secondary to the increased metabolism and not as incident to the anatomic defect of the aorta. It differs thus from the increased cardiac output observed in cases of benign hypertension.

Blood Pressure.—The arterial blood pressures in the extremities were measured by the Tycos recording sphygmomanometer. The values obtained with the patient in the recumbent position were as follows: right brachial artery, 162 systolic and 81 diastolic; left brachial artery, 176 systolic and 98 diastolic; right femoral artery, 109 systolic and 80 diastolic; left femoral artery, 113 systolic and 78 diastolic. The high pulse pressure in the arms is explicable on the basis of the relatively free anastomoses present, which would allow a sudden outflow of blood from the arterial system and be equivalent to a marked reduction of the peripheral resistance.

1. Abbott, M. E.: Coarctation of the Aorta, in Osler, William, and McCrae, Thomas: *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 772. Blackford, L. M.: Coarctation of the Aorta, *Arch. Int. Med.* **41**:702 (May) 1928. Eppinger, E. C., and Midelfart, P. A. H.: Stenosis of the Isthmus (Coarctation of the Aorta), *Am. J. M. Sc.* **185**:528, 1933. Evans, W.: Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch, *Quart. J. Med.* **2**:1 (Jan.) 1933. King, J. T., Jr.: Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, *Arch. Int. Med.* **38**:69 (July) 1926.

2. Grollman, A.: *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

3. DuBois, E. F.: *Basal Metabolism in Health and Disease*, ed. 2, Philadelphia, Lea & Febiger, 1927.

In this patient, part of this excessively high pulse pressure may be attributed to the existence of the aortic insufficiency described.

The basal pulse rate varied from 80 to 84. Thus, the systolic output was 60 cc., which is the normal average.² The increase in pulse rate observed in the patient was, therefore, proportional to the increased cardiac output and resulted in the maintenance of a normal output per beat.

The cardiac work was increased in our subject as a result of the increase in its capacity factor (the cardiac output) as well as the increase in arterial tension against which the heart was laboring. The observed cardiac hypertrophy (a minor degree of which was already present in the patient) is thus attributable to this overwork, and the ultimate development of decompensation in coarctation is to be expected on the same basis as it occurs in other conditions, e. g., in hyperthyroidism, accompanied by a long-continued overworking of the heart. The overwork in our patient was occasioned, however, by two factors: the increased demands occasioned by an elevated metabolic rate and the mechanical effect of expelling this increased amount of blood against an elevated arterial pressure, necessitated in order to supply the lower part of the body with blood and to overcome the effects of the aortic insufficiency.

The metabolic rate of our patient was definitely elevated. The oxygen consumption measured on three occasions at weekly intervals was 300, 306 and 308 cc. per minute, an average of 305 cc. His oxygen consumption, calculated according to the Aub-Dubois standards (39 calories per square meter of body surface),³ was 265 cc., corresponding to a basal metabolic rate in the patient of +15 per cent.

Little attention has been paid in previous studies to the basal metabolic rate in patients with coarctation of the aorta, although it has been reported as elevated in several cases. It is interesting to note that such patients are sometimes considered to be suffering from hyperthyroidism. Although this confusion has been attributed to the warm and suffused condition of the skin of the face and upper extremities, it is possible that the actual existence of a moderate degree of hyperthyroidism may be in part responsible for the confusion noted.

Although it is hazardous to draw conclusions from a single study, it may be suggested that an abnormally active circulation (due to the hypertension) through the thyroid gland might lead to a hyperemia of this organ with a consequent physiologic hyperactivity. It is interesting to note in this connection, too, that approximately 20 per cent of the patients with essential hypertension studied by Boothby and Sandiford⁴ exhibited a basal metabolic rate of over +10 per cent. Whether our patient whose case is reported belongs to this group as regards the etiology of his elevated basal metabolic rate is problematic.⁵

4. Boothby, W. M., and Sandiford, I.: Basal Metabolism, *Physiol. Rev.* 4:69, 1924.

5. In a recent paper, H. L. Ulrich (*Am. Heart J.* 7:641, 1932) reported hyperthyroidism in two of his three cases of coarctation of the aorta of the adult type. He offers an explanation similar to that just discussed to explain the cause of this hyperactivity of the thyroid. Ligation of the inferior thyroid arteries, as suggested by Ulrich, would not only relieve the symptoms of hyperthyroidism, but would also reduce the basal cardiac work and thus relieve the extra myocardial strain to which patients with an elevated metabolism are subjected.

COMMENT

The findings are in accord with what might be anticipated from the clinical state of our patient. His heart is capable of overcoming the anatomic defects by expelling its blood at a high pressure which, in the presence of an adequate collateral circulation, permits a normal supply of blood to the entire body. There is probably an excessive supply to the head and the upper extremities. This is balanced by an approximately equal (as judged from the value of the cardiac output) diminution of blood supply to the lower part of the body.

Our observations are in accordance with the finding of a normal arteriovenous oxygen difference in the legs of a patient with coarctation by Blumgart, Lawrence and Ernstene.⁶ Our findings obviously speak against the view that the pressure in the carotid sinus or in other central regulatory mechanisms exerts any considerable influence on regulation of the cardiac output. Were this the case, one would expect a diminished output in coarctation of the aorta. On the other hand, the normal value of the arteriovenous oxygen difference in our patient indicates this to be the more fundamental factor in controlling the circulation. The metabolic needs of the integral parts of the entire body determine their circulatory supply of blood, and the cardiac output responds to this demand.²

6. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coarctation (Stenosis of the Isthmus) of the Aorta of the Adult Type, *Arch. Int. Med.* **47**:806 (May) 1931.

MYASTHENIA GRAVIS

THE EFFECT OF TREATMENT WITH GLYCINE AND EPHEDRINE; THIRD REPORT

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ROCHESTER, MINN.

It is unnecessary to review the history of the recognition of myasthenia gravis as a clinical syndrome or to enter into details concerning the symptoms, course and prognosis of the disease. The variations in intensity are well known, as are the inconstancy in the rapidity with which the characteristic symptoms of the disease progress, the frequency of the partial remissions during slow but certain progression to a fatal issue and the rarity of complete intermission or spontaneous cure. It may not be generally realized that the disease is by no means rare; that the early stages, sometimes lasting for years, are often overlooked, and that the condition is recognized only in the later stages, which are followed rather rapidly by death, hastened by inhalation pneumonia and inanition.

The etiology of myasthenia gravis is not known. The evidence, however, substantiates the idea that the weakness accompanying the disease is due to disturbance of the intermediate chemical reactions concerned with muscular contraction, or to recovery therefrom. The fact that certain groups of muscles having a more or less common innervation are involved leaves the possibility open that the trophic nerves are in some unknown way involved in the syndrome. The frequency of a history of a sore throat or respiratory infection preceding the first attack may be significant.

No method of treatment of this disease proved of avail until Edgeworth¹ accidentally discovered the value of ephedrine for this purpose.

The second step in advance in the treatment of myasthenia gravis has resulted from the use of glycine. The possibility that glycine might prove beneficial was suggested by the report of Thomas, Milhorat and

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Read before the Association of American Physicians, Washington, D. C., May 9, 1933.

1. Edgeworth, Harriet: A Report of Progress in the Use of Ephedrine in a Case of Myasthenia Gravis, *J. A. M. A.* **94**:1136 (April 12) 1930; The Effect of Ephedrine in the Treatment of Myasthenia Gravis: Second Report, *ibid.* **100**: 1401 (May 6) 1933.

Techner² on its favorable action in progressive pseudohypertrophic muscular dystrophy. I have made two reports³ on the results obtained by the use of glycine and ephedrine. Remen⁴ has also reported on the beneficial effects of administration of glycine to patients with myasthenia gravis.

Glycine is one of the simpler amino-acids, and therefore, is one of the constituents of most proteins, including muscle protein. Since our bodies have, under normal conditions, the ability to synthesize this substance, it is probable that the substance is exceedingly important for many different purposes. Just how it is beneficial in myasthenia gravis is not known; neither is it known why or how ephedrine produces a beneficial effect. Much also remains to be learned about the early diagnosis as well as the ultimate prognosis of this disease.

In the last year, in the Mayo Clinic twelve patients with myasthenia gravis have been closely observed, and personal reports on about as many more who have been treated elsewhere gave the information that a large proportion have improved definitely.

All the cases I observed can be accepted as typical and true examples of the disease, as the diagnosis was corroborated by several members of the Section on Medicine and by the members of the Section on Neurology of the clinic. The disease varied in intensity, and for the purpose of brief presentation the twelve cases may be placed in four groups, depending on the severity of the condition at the time the patients came under observation. Seven of the patients were men and five were women.

GROUPS OF CASES

Group 1 (Four Cases).—Two of the patients were men and two were women. The chief weakness exhibited by this group was in the muscles of deglutition; there was only slight weakness in the muscles of the extremities. The patients were all able to be up and about, but they had difficulty in eating solid food and were troubled with a consid-

2. Thomas, Karl; Milhorat, A. T., and Techner, Fritz: Untersuchungen über die Herkunft des Kreatins. Ein Beitrag zur Behandlung progressiver Muskelatrophien mit Glykokoll, Ztschr. f. physiol. Chem. **205**:93, 1932. Milhorat, A. T.; Techner, Fritz, and Thomas, Karl: Significance of Creatine in Progressive Muscular Dystrophy and Treatment of This Disease with Glycin, Proc. Soc. Exper. Biol. & Med. **29**:609 (Feb.) 1932.

3. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:557 (Sept. 28) 1932. Boothby, W. M.; Adams, Mildred; Power, M. H.; Edgeworth, Harriet; Moersch, F. P.; Woltman, H. W., and Wilder, R. M.: Myasthenia Gravis: Second Report on the Effect of Treatment with Glycine, Proc. Staff Meet., Mayo Clin. **7**:737 (Dec. 28) 1932.

4. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudo-paralytica, Deutsche Ztschr. f. Nervenhe. **128**:66, 1932

erable quantity of the thick mucus in the larynx, which is a more or less characteristic accompaniment in the so-called bulbar type of the disease. The two men had marked ptosis of the eyelids and weakness of the muscles of the eyeball. One of the men and one of the women had been treated with ephedrine $\frac{3}{8}$ grain (0.02 Gm.), two or three times daily, for more than a year before their admission to the clinic. At first the ephedrine had caused considerable improvement; this, however, was not maintained. With the addition of glycine in doses, varying between 20 and 30 Gm., further improvement resulted. At the time of writing, eight months later, the man, aged 64, is in good condition; he is able to work and to eat without much difficulty. The woman, aged 35, is able to continue her work as a secretary. During the last two or three months they have been able materially to decrease the amount of ephedrine and of glycine taken daily, without any aggravation of symptoms.

The other two patients, a man aged 69 and a woman aged 37, started treatment at about the same time. The dosage was ephedrine, $\frac{3}{8}$ grain twice daily, and glycine, 30 Gm. daily. The man is in good condition for his age, and during the winter successfully passed through two severe colds. The woman has been able to continue her work as a secretary without much difficulty. During the last two or three months both have required less glycine and less ephedrine.

Thus the condition of these four patients has improved definitely, and although they cannot be considered cured, they are able to carry on their lives in a reasonably comfortable and happy manner.

Group 2 (Five Cases).—In this group, weakness of the muscles of deglutition was marked; the muscles of the extremities were also weak. All the patients had difficulty in chewing and swallowing, trouble with mucus, and ptosis of the eyelids; they were able to walk only a short distance alone without falling.

One of the patients, a man aged 38, who was given ephedrine, $\frac{3}{8}$ grain twice daily, and glycine, 30 Gm. daily, improved greatly. From being unable to walk a block alone, he now walks 5 or 6 miles, rests ten or fifteen minutes and then walks back. He can run several blocks. One day he shoveled snow for two hours without undue fatigue. He has regained normal strength in his arms and hands. He eats without difficulty. In the last few months he has taken much less glycine and ephedrine; but he found that if he reduced the doses below a certain amount he became weaker.

The second patient, a man aged 56, was even weaker at the time of examination than the first patient, in part due to loss of weight as a result of difficulty in swallowing. He was given ephedrine, $\frac{3}{8}$ grain twice daily, and glycine, 15 Gm. twice daily. His condition remained

stationary for three weeks, then started to improve rapidly. At the end of four months he had gained about 40 pounds (18.1 Kg.), was able to walk eight or ten blocks, and to carry on relatively light work as an electrician for a public service corporation. He, too, has been able to reduce the amount of glycine and ephedrine required to maintain his strength.

The third patient was a man, aged 38, who was unable to walk alone more than one or two blocks and who had moderate difficulty in swallowing. In two months this patient was able to return to his work as a driver of a laundry delivery truck throughout the cold winter. His treatment started with a dose of 30 Gm. of glycine daily. Ephedrine was tried for three days only; it made him worse; so it was discontinued. Recently he has been reducing the amount of glycine until now he takes about 10 Gm. daily. In a letter received a week before this article was written he urgently requested that more glycine be sent quickly, as his supply was low and he was becoming quite weak on a reduced dose. We have not yet heard of the effect of again increasing the dose.

The fourth patient was a schoolgirl, aged 18, who was able to walk only a block or two with the support of her mother's arm. She had difficulty in swallowing and was particularly troubled with mucus. She received both glycine and ephedrine in the usual doses and regained strength rapidly. She is now able to resume her school work, and to lead a reasonably normal life. Usually, however, just before her menstrual period she is barely able to carry on her school work.

The last patient in this group was a woman aged 79. She was very weak, was unable to be out of bed, and had great difficulty in eating. She was given ephedrine for two months and her condition improved definitely; it then seemed to become stationary. Glycine was added to the treatment, and further improvement occurred. The patient is now able to eat soft foods easily, has little mucus, is up and about her room for several hours a day, and occasionally goes outdoors.

Group 3 (One Case).—The patient in this case is Dr. Edgeworth, with whose long fight against myasthenia gravis all are undoubtedly familiar. As is known, she discovered the value of ephedrine in the treatment of this disease. As the result of her skilful treatment of her own condition with ephedrine she was able to transform herself from a bedridden patient to a person able to carry on a reasonably active life. She can walk short distances; she eats well and, except at menstrual periods, she is up and about the house and garden all day and can travel extensively. During the last six months she has also been taking glycine, but has not observed marked alteration in the rate of improvement, which has been steady, although, slow, during the last two years.

Group 4 (Two Cases).—The two men in this group, aged 43 and 24 respectively, did not respond as favorably as the others, either to glycine or to ephedrine during a period of four or five months. One of the patients came to the clinic in the latter part of December, 1932. The first definite symptoms had occurred a month previously; prodromal symptoms could be traced back another six months or more. The disease was in a rapidly progressing stage; each day the condition was noticeably worse. The patient was barely able to walk and he swallowed with great difficulty. Glycine, in doses of 30 Gm. daily, was started on January 4, and ephedrine, $\frac{3}{8}$ grain twice daily, on January 16. Slight improvement was noted on January 18, when the patient insisted, against advice, on riding to South Dakota to attend to business. He returned a week later very much worse, and was having rather frequent attacks of marked dyspnea. The cause of this dyspnea was not determined until January 30, when I found him on the floor in a knee-chest position with a "crooning" respiration. Examination disclosed a large flabby epiglottis hanging down over the larynx and acting as a flap valve. Tracheotomy relieved the obstruction, but the respiratory muscles had become so exhausted in the struggle that artificial respiration by manual methods was necessary while he was being placed in the Drinker respirator. He was in the respirator twenty-two days; after the first eight days he could dispense with the respirator an increasing number of hours each day. He was fed by a Rehfuß tube through the nose.

By March 9 the patient had improved sufficiently to go to an apartment in town. He was up and about the room each day. He breathed easily through the tracheotomy wound and was still given nourishment through the Rehfuß tube. He caught cold and the favorable progress was halted, and finally a slow, gradual decline set in. He became nervous, irritable, and hard to feed; he gave up all hope of recovery and refused to co-operate in the treatment, although the degree of muscular weakness was by no means as marked as at the previous low point. He continued to receive glycine and ephedrine in practically the same doses; moderate variations in dose caused no demonstrable change. In the hope that insulin might be beneficial this was given for a few weeks, in doses increasing to 40 units, but without benefit. Also, in the hope that the administration of creatine would be beneficial, this was given in 1 Gm. doses for a week. The ingested creatine was largely but not entirely excreted during this time, which was in contrast to the little that was excreted following a single dose before the treatment with glycine was started. During the period in which creatine was administered the patient became more nervous, irritable, less co-operative and despondent. He died on April 27, 1933, from causes not directly attributable to the myasthenia syndrome.

Dr. Robertson made a detailed postmortem examination, and I include a brief abstract of his report. The postmortem examination did not reveal thymic or suprarenal tumor, or other gross abnormality. The brain, cord and nerve fibers were not demonstrably abnormal. The muscles, particularly of the thorax and extremities, were fully developed and had a good color. The muscles around the larynx were definitely atrophic and pale. Microscopic examination of these muscles disclosed patchy or interstitial atrophy of the fibers, and infiltration with lymphocytes and reticular cells. Degenerative or fatty changes in the fibers were not outstanding. The muscles of the thoracic wall and diaphragm were much less involved than those of the larynx. In the cortex of the kidneys there were eleven small nodules, about 2 to 4 mm. in diameter, which were composed of masses of lymphocytes with a center core of eosinophils. Parasites, necrosis or other significant changes could not be observed in these nodules. The cultures of the muscles and of the blood in the heart were uniformly negative.

The second patient in this group had had what was apparently an unrecognized mild attack several years ago from which he had almost completely recovered. In the last year the symptoms recurred and recently quite rapidly. On his arrival at the clinic about Feb. 14, 1933, he presented the typical symptoms of severe progressing myasthenia gravis with marked difficulty in swallowing and weakness of the extremities. For several weeks he had been confined to bed during the greater part of the day, and had been taking $\frac{3}{8}$ grain of ephedrine from three to four times daily. During his first twenty days at the clinic the nitrogen balance was determined. He was rapidly losing weight, and was in definite negative nitrogen balance. Before treatment with glycine was started, the negative nitrogen balance was about 3 Gm. daily, and even with the addition of 30 Gm. of glycine daily the nitrogen balance still remained negative to about the same extent. In spite of treatment, difficulty in swallowing became so great that the patient was fed by a Rehfuß tube in the hope of giving enough food to decrease the negative nitrogen balance. It was impossible to determine the nitrogen balance again, but since after intake of food was increased the general condition did not become materially worse, the negative nitrogen balance probably decreased. In the last three months the patient's condition has shown slight fluctuation, but with no definite trend in either direction.

SUMMARY

Of twelve patients with myasthenia gravis treated with ephedrine and glycine, ten have shown definite improvement; four of these have shown marked improvement. Two did not respond to treatment except that the progress of the disease was apparently arrested; one of the two died from causes not directly attributable to the myasthenic syndrome.

I feel sure that by the careful use of either ephedrine or glycine, and more often of both, the condition of most patients with myasthenia gravis can be improved sufficiently to permit them to return to work or at least to enjoy a useful life. Time alone will tell whether this improvement can be maintained. The disease occurs much more frequently than is generally supposed.

ABNORMALITIES OF CALCIUM DEPOSITION IN DIABETES MELLITUS

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The occurrence in the George F. Baker Clinic recently of two cases of compression "fractures" or crushing of the vertebrae with generalized decalcification of bones focused our attention anew on the question of calcium metabolism in diabetes. The subject is of importance both to doctors and to patients. Thus, one of the patients referred to made her illness the basis of a lawsuit in which she sued a physician in her home city, maintaining that improper treatment of the diabetes was the cause of her disability. The importance of information as to the incidence of decalcification of bone in diabetes is obvious. The possibility also exists that with a growing tendency in some clinics, both in America and abroad, toward the use of diets extremely low in fat, cream may be withdrawn from the dietary, and it may be forgotten that unless milk, whole or skimmed, is supplied, the calcium requirement of the body will probably not be met. A lack of calcium can prove serious both for the aged and for the growing child.

REPORT OF CASES

CASE 1.—A Jewish housewife, 62 years old, with diabetes of ten years' duration, was admitted to the New England Deaconess Hospital on Sept. 9, 1932, because of backache of eight months' duration. Physical examination showed signs of loss of weight and advanced kyphosis with marked tenderness and hyperesthesia of the skin over the spine and muscles lateral to it in the lower dorsal and upper lumbar region. Roentgenograms revealed generalized decalcification of bones with crushing of the seventh and eight dorsal and first lumbar vertebrae. No evidence of a malignant condition was found. The arteries of the arms and legs showed a high degree of calcification, as did the descending aorta. The blood serum calcium was 10 mg., and the phosphorus, 3.7 mg., per hundred cubic centimeters.

CASE 2.—An Irish housewife, 77 years of age, with diabetes for eighteen years, entered the New England Deaconess Hospital on Nov. 8, 1932, because of persistent pain in the back which had been present for three days following a minor jolt in an automobile. For ten years she had lived alone, preparing her own meals; she stated, however, that she had drunk a quart of milk a day for years.

From the George F. Baker Clinic, Director, Elliott P. Joslin, M.D., New England Deaconess Hospital, Boston.

Physical examination on admission showed marked tenderness over the middle of the back. Roentgenograms showed generalized decalcification of the bones with a compression fracture of the fifth thoracic vertebra. There was visible calcification in the arteries of the extremities and in the aorta. The blood serum calcium was 9.4 mg., and the phosphorus, 2.8 mg., per hundred cubic centimeters on Nov. 10, 1932. On December 5, after almost a month of administration of calcium gluconate and viosterol, these values were 10.5 mg. and 3.8 mg. per hundred cubic centimeters, respectively. On December 5 the total protein of the blood serum was found to be 7.6 Gm. per hundred cubic centimeters.

Treatment in both cases was carried out with the advice of Dr. Mark H. Rogers. It consisted at first of rest in bed with hyperextension and the subsequent use of braces, combined with a diet high in calcium, calcium gluconate and viosterol. Partial relief from pain and gradual return to greater activity were obtained in both instances. Roentgenograms of the bones will be taken at intervals in an effort to demonstrate deposition of calcium. It is interesting that in case 1, despite clinical improvement, films taken on April 21, 1933, seven months after the first roentgenograms were taken, showed no change.

FREQUENCY OF OSTEOPOROSIS IN DIABETES

These two cases are the only instances of osteoporosis with crushing of the vertebrae which have been recognized among 12,000 patients who have applied for diagnosis or treatment of diabetes over a period of thirty-five years. Except for the report of Morrison and Bogan,¹ who found delayed development of bone, narrowness of the shaft and thinness of the cortex with atrophy of the bone in some cases of diabetes in children, no systematic study of roentgenograms of bones of persons with diabetes is known to us. At present no accurate statement is possible as to whether or not decalcification of bone is more common in persons with diabetes than in persons without diabetes. In any such comparison, proper attention must be given to the age of the patient, his activity and the amount of calcium in his diet.

It is true that in some patients fractures have seemed to occur with slight trauma. For example, one patient, while alternately raising and lowering his feet on a bath mat, felt a sudden pain in one foot; a roentgenogram showed a fracture of the second metatarsal bone. Another, aged 28 years, with diabetes of two years' duration, undergoing extreme undernutrition, fell from a low bed and fractured a rib. She began treatment with insulin in December, 1922, and is now in excellent condition. When in the hospital a patient while walking slipped to the floor (covered with a rubber flooring material) and fractured his skull. Another patient, while walking, turned his ankle and fell, striking the

1. Morrison, L. B., and Bogan, I. K.: Bone Development in Diabetic Children: A Roentgen Study, *Am. J. M. Sc.* **174**:313 (Sept.) 1927.

side of his left hand on the floor, thereby fracturing the fifth metacarpal bone. At the autopsy of another person, who died at the age of 54 years with diabetes of seven months' duration, the ribs were found to be so fragile that they could be snapped in two between the thumb and two fingers. Other known cases of fractures which followed greater trauma have not been cited, because our data do not allow an accurate statement as to the incidence of broken bones in the general diabetic series.

Although only one case cited occurred in the period before treatment with insulin, in every case diabetes had existed for long periods without treatment with insulin or adequate dietary treatment, so that it is probable that these patients had suffered from mild acidosis or incompletely controlled diabetes at intervals over a prolonged period. It is well recognized that in diabetic acidosis, as in acidosis due to other causes, there is an increased excretion of calcium in the urine. This was early demonstrated by Joslin² and substantiated by careful recent work such as that by Atchley and his associates.³

From a review of the older literature one would infer that in diabetes mellitus in general there is an increased excretion of calcium. Thus, von Noorden⁴ mentioned that such findings were reported by Böcker, Neubauer, Toralbo, Gerhardt, von Moraczewski, and others, including workers in his own laboratory. Falta and Whitney,⁵ from experiments on depancreatized dogs, believed that the negative calcium balance and the calcium excretion which were observed were out of proportion to any degree of acidosis present. Somewhat more recently (but still before the time when strict control of diabetes by insulin became possible) Kahn and Kahn⁶ found a definite negative calcium balance in all of five cases studied.

Although in this clinic the incidence of fractures has been low, other instances of faulty calcium deposition have been noted. Dental consultants state that on the whole the teeth of our children whose diabetes is well controlled with diet and insulin show no abnormal incidence of dental caries, whereas children with diabetes who have

2. Joslin, E. P.: *Metabolism in Diabetic Coma, with Especial Reference to Acid Intoxication*, J. M. Research **6**:316 (Nov.) 1901.

3. Atchley, D. W.; Loeb, R. F.; Richards, D. W. Jr.; Benedict, E. M., and Driscoll, M. E.: *On Diabetic Acidosis. A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy*, J. Clin. Investigation **12**:297 (March) 1933.

4. von Noorden, C.: *Metabolism and Practical Medicine*, Chicago, W. T. Keener & Co., 1907, vol. 3, p. 600.

5. Falta, W., and Whitney, J. L.: *Zur Kenntnis des Eiweiss- und Mineralstoffwechsels pankreatischer Hunde*, Beitr. z. chem. Phys. u. Path. **11**:224, 1908.

6. Kahn, M. and Kahn, M. H.: *Lime Deficiency of Diabetes*, Arch. Int. Med. **18**:212 (Aug.) 1916.

had coma or for other reasons must be regarded as poorly controlled have had extreme dental caries, and in at least one instance all the teeth had been lost by the time the patient had reached the age of 17. In a study of roentgenograms of 100 young persons with diabetes, 11 showed atrophy of bones.⁷ It is only fair to add that this atrophy occurred among juvenile patients who had been treated for long periods without insulin. Atrophy of bones was observed in the years from 1924 to 1926 inclusive, and then disappeared. Dwarfism and roentgen evidence of transverse striae and delayed closure of epiphyses also occurred in this group.

ABNORMAL LOCAL DEPOSITS OF CALCIUM

Paradoxically, in the 2 patients with crushing of the vertebrae there existed extensive arteriosclerosis, with deposits of calcium in the peripheral arteries and the aorta. Such instances of extensive localized deposition of calcium are all too common in persons with diabetes. In the days before insulin was used, calcification of the arteries, demonstrable by roentgenogram or at autopsy, was the rule in patients with diabetes of more than five years' duration. Among 70 children with diabetes of seven or more years' duration, calcification of the arteries of the legs was demonstrated in 30 per cent. Morrison and Bogan⁸ demonstrated that among 62 persons with diabetes of ten years' standing, 91 per cent had calcified peripheral arteries. Lehnherr⁹ reported from the New England Deaconess Hospital that the aortas of patients with diabetes dying after the age of 50 on the average contained three times as much calcium as aortas of persons not having diabetes dying at a comparable age. The coronary vessels were found by Nathanson¹⁰ to show calcification four times as often in persons having diabetes as in those not having it.

Localized deposits of calcium in the corium of the skin of patients with diabetes have occasionally been noted and will be the subject of a forthcoming paper by Drs. A. H. Davis and S. Warren of the pathologic laboratory of the New England Deaconess Hospital.

Cataracts in ocular lenses are known to contain in the advanced stages large amounts of calcium.¹¹ Among 294 young persons with

7. White, P.: *Diabetes in Childhood and Adolescence*, Philadelphia, Lea & Febiger, 1932, p. 126.

8. Morrison, L. B., and Bogan, I. K.: *Calcification of the Vessels in Diabetes; Roentgenographic Study of Legs and Feet*, J. A. M. A. **92**:1424 (April 27) 1929.

9. Lehnherr, E. R.: *Arteriosclerosis and Diabetes Mellitus*, New England J. Med. **208**:1307 (June 22) 1933.

10. Nathanson, M. H.: *Coronary Disease in One Hundred Autopsied Diabetics*, Am. J. M. Sc. **183**:495 (April) 1932.

11. Updegraff, H.: *Calcium, Phosphorus and Cholesterol in Cataractous vs. Apparently Normal Lenses from Human Eyes*, Proc. Soc. Exper. Biol. & Med. **29**:964 (May) 1932.

diabetes, under 20 years of age, examined at the New England Deaconess Hospital by Drs. J. H. Waite and W. P. Beetham,¹² 3.8 per cent have shown progressive changes in the lens and an additional 1.1 per cent have shown less definite changes of this nature. Among 245 persons with diabetes over 30 years of age, examined at necropsy, Warren¹³ found 25.3 per cent to have gallstones, as opposed to 13.5 per cent in 400 persons of similar ages not having diabetes. Pancreatic calculi have been discovered in 3 persons by roentgenogram and at autopsy in 3 additional cases. Wilder¹⁴ reported 3 such cases among 58 autopsies on persons with diabetes. In their report of autopsies on 25 persons with pancreatic calculi, Ackman and Ross¹⁵ stated that 10, or 40 per cent, had glycosuria. Morrison and Bogan¹⁶ described pancreatic calculi in 8 cases in which 4 of the patients had diabetes.

FACTORS INFLUENCING CALCIUM AND PHOSPHORUS METABOLISM

Factors which might be operative in diabetes are: (1) age of the patient; (2) activity of the patient; (3) amount of lime salts in diet; (4) great excess in diet of calcium over phosphorus, and vice versa; (5) achlorhydria or hypochlorhydria and diminished or lacking pancreatic lipolytic ferment, two conditions frequently found in diabetic patients (either deficiency may be associated with diarrhea and this may prevent a proper absorption of calcium); (6) prolonged diarrhea from other causes; (7) prolonged acidosis; (8) excessive fat in the diet, particularly if unabsorbed (it is true that Mallon and her co-workers¹⁷ found that in 2 normal subjects the amount of fat in the diet had no definite influence on the retention of calcium; their high fat diet, however, actually contained on the average only 105.6 Gm. of fat per day, and, furthermore, the studies made by these authors were of very short duration); and (9) deficient or excessive supply of vitamin D substances. An interesting suggestion is that possibly the hypercholesteremia so frequently observed in persons with

12. Waite, J. H., and Beetham, W. P.: Unpublished data.

13. Warren, S.: *The Pathology of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1930, p. 106.

14. Wilder, R. M.: *Necropsy Findings in Diabetes*, *South. M. J.* **19**:241 (April) 1926.

15. Ackman, F. D., and Ross, A.: *Pancreatic Lithiasis*, *Surg., Gynec. & Obst.* **55**:90 (July) 1932.

16. Morrison, L. B., and Bogan, I. K.: *Pancreatic Calculi*, *New England J. Med.* **199**:1129 (Dec. 6) 1928.

17. Mallon, M. G.; Jordan, R., and Johnson, M.: *A Note on the Calcium Retention on a High and Low Fat Diet*, *J. Biol. Chem.* **88**:163 (Aug.) 1930.

diabetes is associated with an increase in ergosterol, which, if activated, may increase the deposit of calcium in diabetic arteries or elsewhere.¹⁸

DAILY REQUIREMENT OF CALCIUM

Sherman's¹⁹ figures place the desired amount of calcium in the daily diet for the average adult at 0.68 Gm., and for the growing child at 1.0 Gm. The desirable amount of phosphorus is stated as 1.32 Gm. a day. These figures were derived from metabolic studies on normal persons. To the average minimum intake found capable of preventing a negative calcium balance Sherman added 50 per cent to secure the figures cited. Naturally, therefore, it may be that with a great many persons these figures allow a very liberal margin of safety, thus explaining why instances of osteoporosis are not more common in those who have lived on a nonsupervised diet containing considerably less lime salts than the theoretical optimum amount.

CALCIUM IN DIABETIC DIETS

From a study of several representative diets given to patients at the New England Deaconess Hospital it was found that the "basic" diet (i. e., the diet exclusive of milk, cream and cheese) averages about 0.4 Gm. of calcium a day. It is therefore inadequate. However, by merely adding a glass (180 cc.) of milk and 120 cc. of 20 per cent cream or 15 Gm. of cheese and 150 cc. of 20 per cent cream, one can easily satisfy the calcium requirement. It is difficult to do this unless use is made of dairy products or eggs, since other foods have a relatively low calcium content. Sherman has shown, too, that calcium in vegetables is not as effectively absorbed or utilized as that in milk. Although Mallon and her associates²⁰ more recently demonstrated that fresh green lettuce is a satisfactory source of calcium, the quantities which must be ingested are large.

The amount of calcium in calcium-rich foods may be remembered easily if the following values are kept in mind. Approximately 0.1 Gm. of calcium is contained in each of the following foods: milk, 86 Gm. (about 3 oz.); cream (20 per cent), 108 Gm. (about 4 oz.); cheese, 11 Gm. (about $\frac{1}{3}$ oz.); eggs, 3.

18. Rabinowitch, I. M.: Observations on the Significance of the Cholesterol Content of the Blood Plasma in Diabetes Mellitus, *Canad. M. A. J.* **28**:162 (Feb.) 1933.

19. Sherman, H. C.: Phosphorus Requirement of Maintenance in Man, *J. Biol. Chem.* **41**:173, 1920; Calcium Requirement of Maintenance in Man, *ibid.* **44**:21, 1920; *Chemistry of Food and Nutrition*, New York, The Macmillan Company, 1932, chaps. xiii and xxiii.

20. Mallon, M. G.; Johnson, L. M., and Darby, C. R.: The Calcium Retention on a Diet Containing Leaf Lettuce, *J. Nutrition* **6**:303 (May) 1933.

An excellent plan is that, followed in the Indiana University Hospitals at Indianapolis²¹ and in other institutions, of providing special columns on the diet sheet of diabetic patients for recording the amount of calcium and phosphorus given the patient, along with the figures for carbohydrate, protein and fat. If the calcium requirement is met, one need not be greatly concerned with the phosphorus content of the diet, since the two elements accompany each other in most foods.

COMMENT

Sufficient data have been presented to show that various types of abnormalities of deposition of calcium are found in diabetes mellitus. On the one hand, there are conditions of lack of calcium which are due, we believe, either (1) to lack of lime salts or vitamin D in the diet or to other causes operative as well in the person without diabetes or (2) to prolonged acidosis. There is little or no evidence in recent literature to suggest that in patients with well controlled diabetes there is any significant disorder of calcium metabolism attributable to the diabetes itself. Indeed, von Noorden⁴ quotes with apparent agreement the statement of Gaethgens that "when there is no acidosis, the calcium metabolism of diabetic patients is the same as that of ordinary people." We have found the calcium and phosphorus content of the blood of patients with controlled diabetes invariably to be normal. It is significant in this connection that while Cammidge²² found a low blood calcium in 44 per cent of his diabetic patients, Kylin²³ reported that his patients have values higher than normal. Wishnofsky²⁴ found, by studying dextrose tolerance curves, that calcium chloride given intravenously did not appear to influence the tolerance of patients with diabetes for dextrose.

On the other hand are the conditions, such as arteriosclerosis, cataracts and calculi of various sorts, in which calcium salts are deposited in excess locally. As yet no one has brought forward proof that these are to be regarded as disorders of calcium metabolism per se. These abnormalities of calcium deposition which are so often associated with serious clinical consequences seem therefore to depend on the duration and severity of the diabetes and to be controllable chiefly by its early, adequate and prolonged treatment.

21. Rudesill, C. L.: Personal communication.

22. Cammidge, P. J.: Retinitis in Diabetics, *Proc. Roy. Soc. Med. (Sect. Ophth.)* **23**:24 (Jan.) 1930.

23. Kylin, E.: Ueber den Kalkumsatz bei Diabetes mellitus, *Acta med. Scandinav.* **66**:197, 1927.

24. Wishnofsky, M.: Studies in Calcium and Carbohydrate Metabolism; Calcium and Glucose Tolerance in Diabetes Mellitus, *J. Lab. & Clin. Med.* **13**: 133 (Nov.) 1927.

In the present state of knowledge, treatment must provide adequate calcium and phosphorus in the diet regardless of theoretical considerations that by so doing localized calcifications may be favored. We regard it essential to provide for all patients, particularly growing children, the optimum amount of lime salts in the daily diet. This should be supplemented, when indicated, by appropriate doses of cod liver oil, halibut liver oil or viosterol.

LIVER EXTRACT THERAPY IN CIRRHOSIS OF THE LIVER

RELATION OF LIVER DYSFUNCTION TO NONSTORAGE OF "ANTI-ANEMIC" SUBSTANCE IN PRODUCING A BLOOD PICTURE RESEMBLING PERNICIOUS ANEMIA IN A PATIENT SECRETING FREE HYDROCHLORIC ACID

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The following case is reported in the hope that it may possibly throw new light on a group of patients who have been described as having a blood picture resembling that of pernicious anemia, but who have the ability to secrete hydrochloric acid in their stomachs.

REPORT OF A CASE

History.—R. M., a white man, aged 58, was admitted to the University Hospital on Oct. 27, 1931, complaining chiefly of "pain in the abdomen." Three months previously, he first noted a dragging and generalized discomfort in the abdomen below the umbilicus. This sensation became progressively worse and after nine weeks nausea developed. The pain was not related to the intake of food. Although the patient did not go to bed because of the pain, it was necessary for him to stop working. One week before admission, he noted that his stools were black and watery; he thought that this was the result of medication which was given him for "enlargement of the liver." There had not been hematemesis, jaundice, chills or fever. His appetite was extremely poor, and he had lost about 10 pounds (4.5 Kg.) in weight in three months.

Physical Examination.—The patient showed evidence of recent loss of weight. The skin and the mucous membranes were pale. The teeth showed marked evidence of caries. The heart was of borderline size, regular in action, with a rate of 60 a minute; the blood pressure was 122 systolic and 80 diastolic. The abdomen was distended, and there was marked tenderness over the region just below the umbilicus, less evident in the epigastrium. The liver and spleen were not palpable. The veins of the abdominal wall were slightly distended, suggesting a compensatory collateral circulation.

Laboratory Observations.—The urine and stools showed no abnormalities. Gastric analysis following the injection of 1 mg. of histamine hydrochloride showed free acid in all specimens. The specimen following fasting contained 4 degrees of free acid; and at ten minute intervals the amounts of free acid found were: 15, 74, 87, 61 and 83 degrees. The red cell count was 2,590,000 per cubic milli-

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Read before the Medical Journal Club, University Hospital, Dec. 5, 1932.

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meter; the hemoglobin, 61 per cent (Sahli); the white cell count, 5,850; moderate poikilocytosis was present; 51 per cent of the red cells were larger than 7.5 microns, varying in size from 3.0 to 12.0 microns. Repeated roentgen and fluoroscopic examinations of the gastro-intestinal tract revealed only "fixation and tenderness over the appendix and cecum." The Kahn test was negative.

Course in Hospital.—Because of the pain in the lower part of the abdomen, loss of weight and anemia, an exploratory operation was performed on Nov. 19, 1931, by Dr. E. Potter. The stomach and duodenum were normal so far as could

Data in the Case Reported

Date	Red Blood Cells, Millions per C.Mm.	White Blood Cells, per C.Mm.	Hemo-globin, per Cent	Differ-ential Count*	Reticulo-cytes, per Cent	Day of Treat-ment	Treatment
11/10/31	2.59	9,000	61	
12/14/32	2.22	10,800	41	P. 71.0 E. 1.0 L.L. 12.0 S.L. 9.5 Mon. 6.5	8.7	..	
12/19/32	2.38	7,600	44	Transfusion, 500 cc.
12/20/32	51	
12/22/32	62	Transfusion, 500 cc.
12/26/32	3.09	57	
12/29/32	3.16	11,700	55	2.8	..	
12/30/32	2.68	11,100	48	3.9	0	Intravenous liver extract, 20 cc.
12/31/32	5.2	1	
1/ 1/33	5.3	2	
1/ 2/33	7.9	3	
1/ 3/33	4.6	4	
1/ 4/33	5.1	5	
1/ 5/33	7.9	6	
1/ 6/33	2.75	9,700	49	7.6	7	Intravenous liver extract, 20 cc.
1/ 7/33	8.5	8	
1/ 8/33	9.0	9	
1/ 9/33	10.5	10	
1/10/33	10.5	11	
1/11/33	6.5	12	
1/12/33	6.1	13	
1/13/33	2.47	6,800	41	5.2	14	Intravenous liver extract, 20 cc.
1/14/33	3.7	15	
1/15/33	4.6	16	
1/17/33	1.4	18	
1/19/33	2.06	7,750	44	20	
2/11/33	3.89	12,100	53	43	Intravenous liver extract, 20 cc.
3/ 3/33	3.99	8,800	64	63	

* P. indicates polymorphonuclears; E., eosinophils; L.L., large lymphocytes; S.L., small lymphocytes; Mon., monocytes.

be determined by palpation. The gallbladder was small and contained no stones. The liver showed a moderate degree of cirrhosis without much enlargement. The appendix was fastened by adhesions and appeared to be the site of previous inflammation. It was removed in the routine manner.

The patient felt comparatively well for a few weeks following the operation; then the pain reappeared and became progressively more troublesome. It was dragging, dull and constant and had a tendency to become localized in the lower part of the abdomen. One month previous to his second admission, Dec. 19, 1932, he became aware of increased weakness and shortness of breath, coldness of the lower extremities and numbness and tingling, more marked in the feet than in the hands. His appetite again became extremely poor and the nausea returned, but the patient did not vomit. There was a loss of 20 pounds (9 Kg.) in weight in two months. The data from the physical examination were practically the

same as on the previous visit. Roentgenograms at this time suggested an obstructing carcinoma in the proximal transverse colon.

A second laparotomy was performed by Dr. Potter on Dec. 23, 1932. A rather marked generalized fibrinopurulent peritonitis was found. All the organs examined, except the liver, were essentially normal. There was no evidence of carcinoma of the colon.

Six days after the operation, the patient was admitted to the Simpson Memorial Institute. The blood count at this time was somewhat elevated, owing to two blood transfusions. The red cell count was 3,160,000; the hemoglobin, 55 per cent (Sahli); and the white blood cell count, 11,700. Following treatment with purified liver extract given intravenously, as suggested by Dr. Raphael Isaacs, the reticulocytes, on the tenth and eleventh days, reached a peak of 10.5 per cent. Although the response was somewhat delayed, this is the calculated maximum response for a patient with true pernicious anemia.¹ Thereafter he received similar treatments (a total of four) at weekly intervals, and when last observed, sixty-three days after the initial treatment, his condition was distinctly improved. The red cell count was 3,990,000; the hemoglobin, 64 per cent (Sahli); and the white cell count, 12,100. Details of the blood studies are given in the table.

COMMENT

Castle² has proposed that pernicious anemia may be the result of the absence of an extrinsic factor (possibly vitamin B₂) or the absence of an intrinsic factor in gastric juice. Sturgis and Isaacs³ have shown that stomach tissue alone develops the active principle; Minot and Murphy,⁴ that the active principle is present in liver; and Richter, Ivy, and Kim⁵ have gone a step further and demonstrated that the active principle is stored in the liver.

From these studies, it would appear that the syndrome of pernicious anemia might possibly result from or be produced in three ways: (1) by the absence of the proper food factors; (2) by the absence of the activating secretion in the stomach; (3) by the failure to absorb the product necessary for the maturation of the red blood cells. To these is added a fourth possibility. With the destruction of the liver, the excess of the product essential for the growth of the red cells, produced during digestion, may be lost, owing to the inability of the damaged hepatic tissue to

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2. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* **178**:748 (Dec.) 1929. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, *New England J. Med.* **207**:55 (July 14) 1932.

3. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. A. M. A.* **93**:747 (Sept. 7) 1929.

4. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**:470 (Aug. 14) 1926.

5. Richter, O., Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," *Proc. Soc. Exper. Biol. & Med.* **29**:1093 (June) 1932.

store it, as suggested by the case of cirrhosis of the liver herein presented. It is conceivable that sufficient hematopoietic stimulating material may be manufactured and absorbed to maintain the normal red cell count, but that it cannot be stored for usage during the interval between meals. If this supposition is correct, the red cell count may not be maintained at a normal level, owing to a deficient storage capacity of the liver, but may drop to a low level of from 2,500,000 to 3,000,000 cells, and remain there. With this idea in mind, it would perhaps have been better to give treatments at more frequent intervals in this unusual condition.

The hypothesis of failure or decreased storage would enable one to account for the various etiologic factors which are known to give the picture of pernicious anemia, whether free acid is present or not in the gastric juice. If the stomach is involved, free acid as a rule is not secreted, but if the disturbance is only in absorption⁶ or storage, free acid may possibly be formed. This factor of the disturbance of storage may account for the blood pictures resembling that of pernicious anemia which are seen in the so-called pernicious anemia of pregnancy and other diseases accompanied by macrocytosis.

Cases of cirrhosis of the liver with anemia, a macrocytosis and a color index of 1 or more have been described by Holler and Kudelka,⁷ Cheney and Niemand,⁸ Masina⁹ and others; the mechanism described in this paper is suggested as the possible cause for the specific blood picture.

SUMMARY

1. A case of cirrhosis of the liver is reported in which free hydrochloric acid was present in the gastric contents and in which the blood picture simulated that of true pernicious anemia. The response to intravenous liver therapy was similar to that observed in patients with true pernicious anemia.

2. In addition to factors of defective gastric secretion, defective intake of food and inadequate absorption, a fourth factor in the production of a blood picture resembling that of pernicious anemia is suggested to be the interference of the storage of the material necessary for the maturation of the red blood cells.

6. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* **182**:741 (Dec.) 1931.

7. Holler, G., and Kudelka, O.: Resultate von Bestimmungen des Erythrozytendurchmessers beim Menschen unter physiologischen und pathologischen Verhältnissen, *Folia haemat.* **35**:197 (Nov.) 1928.

8. Cheney, G., and Niemand, F.: The Treatment of Secondary Anemia with "Secondary Anemia Liver Extract" and Iron, *Am. J. M. Sc.* **184**:314 (Sept.) 1932.

9. Masina, N.: Das Blutbild bei Leberzirrhose mit besonderer Berücksichtigung der Monozytengranulation, *Folia haemat.* **46**:335 (March) 1932.

PHYSIOLOGY OF VITAMINS

XXIII. THE EFFECT OF LACK OF THE VITAMIN B COMPLEX ON THE SECRETION OF GASTRIC JUICE IN DOGS WITH GASTRIC POUCHES

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A study of the effect of lack of the vitamin B complex on gastric secretion is of interest for several reasons. The first is based on analogy and is concerned with that vicious circle of pernicious anemia, gastric achylia and subacute combined sclerosis. This group of symptoms has been termed "combined system disease." The relationships of the elements of this syndrome are fascinating in their implications.

It is well recognized that practically all cases of pernicious anemia are characterized by gastric achylia. In support of this view, observations of Minot and Murphy¹ and others indicating that pernicious anemia may well be classified as a deficiency disease, and the findings of Castle² that impaired gastric function plays an important rôle, may be cited. According to some investigators in this field (Hurst and Bell,³ Collier⁴ and Vanderhoof⁵), there is an almost invariable asso-

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Because the diets used in this study were markedly but not absolutely deficient in either vitamin B (B₁) or G (B₂), we use the expression "lack of vitamin B complex."

This paper is a report of some of the data contained in the dissertation presented by Alfred Gilman in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Yale University, 1931.

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2. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* **178**:748, 1929.

3. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, *Brain* **45**: 266, 1922.

4. Collier, J.: Intrinsic Diseases of the Spinal Cord, in Christian, H. A., and Mackenzie, James: *Oxford Medicine*, New York, Oxford University Press, 1921, vol. 6, pp. 327 and 356.

5. Vanderhoof, Douglas: The Etiologic Relation of Achylia Gastrica to Combined Sclerosis of the Spinal Cord, *Arch. Int. Med.* **32**:958 (Dec.) 1923.

ciation of achylia gastrica with combined sclerosis of the spinal cord. Furthermore, in many cases there may be observed lesions of the spinal cord associated with gastric achylia and the absence of an associated anemia as a complicating condition. This has led Hurst and Bell³ and Vanderhoof⁵ to believe that the fundamental cause of spinal sclerosis may be achlorhydria. Treatment of such sclerosis with oral administration of hydrochloric acid has been tried and believed to prove efficacious.

Pathologic findings on dogs that have succumbed to lack of the vitamin B complex were interpreted by Gildea, Kattwinkel and Castle⁶ as indicating degeneration of the spinal cord. The lesions were believed to bear a marked similarity to those associated with achylia gastrica and pernicious anemia. Zimmerman and Burack,⁷ however, failed to confirm these observations. In the work just cited there is a hint that a possible explanation of the neurologic findings associated with a deficiency of the vitamin B complex may be found in a gastric disturbance.

Another reason for the interest in the gastric secretion during lack of the B complex lies in the existence of other gastric symptoms observed during the course of the deficiency. Karr⁸ and Cowgill⁹ demonstrated that dogs lose their normal urge to eat when deprived of this dietary factor. According to Rose, Stucky and Cowgill,¹⁰ gastric motility is usually markedly depressed during the advanced stages of the deficiency. Observations of the secretory activity of the stomach in animals subsisting on diets adequate except for the vitamin B complex would seem, therefore, to be a logical sequel to these studies.

Perusal of the literature reveals that there have been only a few investigations of the influence on gastric secretion of a dietary regimen deficient in the B complex. Danysz and Koskowski¹¹ conducted studies on pigeons which (a) received a normal diet, (b) were starved, (c) received a diet of polished rice, and (d) received polished rice plus a

6. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, *New England J. Med.* **202**:523, 1930.

7. Zimmerman, H. M., and Burack, Ethel: Lesions of the Nervous System Resulting from Deficiency of the Vitamin B Complex, *Arch. Path.* **13**:207 (Feb.) 1932.

8. Karr, W. G.: Some Effects of Water-Soluble Vitamin upon Nutrition, *J. Biol. Chem.* **44**:255, 1920.

9. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin-B and the Nutrition of the Dog, *Am. J. Physiol.* **57**:420, 1921.

10. Rose, W. B.; Stucky, C. J., and Cowgill, G. R.: Studies in the Physiology of Vitamins: XIII. The Relation of Gastric Motility to Anhydremia in Vitamin B-Deficient Dogs, *Am. J. Physiol.* **92**:83, 1930.

11. Danysz, Michel, and Koskowski, W.: Etude de quelques fonctions digestives chez les pigeons normaux, nourris au riz poli et en inanition, *Compt. rend. Acad. d. sc.* **175**:54, 1922.

daily injection of 0.1 mg. of histamine. The integrity of the gastric glands was tested by chemical examination of the gastric secretion subsequent to stimulation with histamine. The responses yielded in groups *a*, *b* and *d* were practically normal. Group *c*, however, exhibited a marked decrease in both volume and acidity of secretion combined with an almost complete loss of peptic activity.

The investigations of Farnum¹² were conducted on dogs possessing Pavlov gastric pouches. The diet offered these animals is not reported. However, it was supposedly rendered free from vitamin B by autoclaving in an alkaline medium. The experimental animals showed a progressively decreasing function of the gastric glands as evidenced by diminished volume and acidity of the secretion. Protocols of the intake of food were not given, but it is highly probable that the decrease in gastric function exhibited by these animals was chiefly a reflection of the anorexia which is characteristic of such a dietary deficiency. It was also reported that the animals receiving the faulty diet were more refractory in their response to histamine, larger doses of this drug being required to produce an effect equal to that characteristic of the animal on a normal dietary regimen. The response of the gastric glands to gastrin was reported as being normal at all times. This might be interpreted as failing to confirm Ivy's¹³ idea that gastrin is histamine.

The experiments of Gildea, Kattwinkel and Castle⁶ were less quantitative. The dogs were divided into three groups and placed on diets believed to be deficient primarily in (*a*) the vitamin B complex, (*b*) antineuritic vitamin B (B_1) and (*c*) vitamin G (B_2). Gastric function was determined by the response to injections of histamine. Dogs with gastric pouches were not used; instead, a single sample of gastric juice was aspirated from the stomach thirty minutes after the gastric stimulant had been injected. These investigators were able to demonstrate the presence of free hydrochloric acid in the secretion of every animal, even when the symptoms of deficiency in vitamins were severe. The juice also had a normal concentration of pepsin. Repeated injections of histamine in no way alleviated or postponed the symptoms characteristic of a B avitaminosis.

As can be seen from these brief summaries of previous investigations, a wide difference of opinion exists as to the ability of the gastric glands to function during a dietary regimen characterized by a deficiency of both the vitamin B complex and its separate B (B_1) and G (B_2) components. In the experiments about to be described, the technic was fundamentally the same as in that used by Gildea, Kattwinkel and

12. Farnum, M. B.: Gastric Secretion in Experimental Beriberi in the Dog, *Arch. Int. Med.* **37**:212 (Feb.) 1926.

13. Ivy, I. C.: Personal communication to the authors.

Castle, who used dogs as the experimental subjects. The animals were provided with gastric pouches of the Pavlov and the Heidenhain type, respectively. Histamine was used as the gastric stimulant.

I. THE EFFECT OF A DIET DEFICIENT IN ANTINEURITIC VITAMIN B
ON THE SECRETION AND CHEMICAL COMPOSITION OF
GASTRIC JUICE

Diet Used.—In the first series of experiments the dogs were fed the casein III diet, details of which have been described elsewhere (Cowgill¹⁴). This ration has been used repeatedly in vitamin studies on dogs and shown to be markedly deficient in the antineuritic B₁ component of the vitamin B complex; in all probability, judging from the observations of Cowgill, Stucky and Rose,¹⁵ it is very low in its content of the heat-stable G (B₂) factor. In view of the facts (*a*) that a much longer time is required to deplete the tissues of vitamin G (B₂) than is the case for the B (B₁) substance (Bing and Mendel,¹⁶ Sherman and Sandels¹⁷ and Graham and Griffiths¹⁸) and (*b*) that subsistence on the casein III diet results in the development of nerve lesions that are characteristic and quite different from those due to lack of vitamin G (B₂) alone (Zimmerman and Burack⁷ and Zimmerman¹⁹), we believe that the phenomena observed in the animals of this series may be definitely attributed to lack of vitamin B (B₁).

Prior to the period of subsistence on this diet alone each animal received a supplement of vitavose²⁰ (1 Gm. per kilogram a day) designed to supply the needed B vitamins. The diet so supplemented is complete in every known respect; dogs subjected to such a dietary regimen have maintained an excellent nutritive condition over a period of three years.²¹

The normal response of the gastric glands of the experimental animals subsisting on this complete ration was first determined. The administration of vitavose was then discontinued, and tests of gastric

14. Cowgill, G. R.: Physiology of Vitamins: II. Parenteral Administration of Vitamin-B—Mammalian Experiments, *Am. J. Physiol.* **66**:164, 1923.

15. Cowgill, G. R.; Stucky, C. J., and Rose, W. B.: The Physiology of Vitamins: V. Cutaneous Manifestations Related to a Deficiency of the Vitamin B Complex, *Arch. Path.* **7**:197 (Feb.) 1929.

16. Bing, F. C., and Mendel, L. B.: The Vitamin B and the Vitamin G Requirements of the Albino Mouse, *J. Nutrition* **2**:49, 1929.

17. Sherman, H. C., and Sandels, M. R.: Further Experimental Differentiation of Vitamins B and G, *J. Nutrition* **3**:395, 1931.

18. Graham, C. E., and Griffiths, W. H.: Vitamins B₁ and B₂ in Tissues of Normal and Experimental Rats, *Proc. Soc. Exper. Biol. & Med.* **29**:695, 1932.

19. Zimmerman, H. M.: Personal communication to the authors.

20. A soluble vitamin B preparation made from wheat germ.

21. Drabkin, D. L.: Personal communication to the authors.

function were made at intervals until the symptoms characteristic of a lack of vitamin B developed in the animals. The ration was then again supplemented with the necessary dietary essential and the gastric secretory power determined during the animal's recovery period.

Gastric Function Tests.—The most physiologic approach to the problem under investigation would be the use, as a gastric stimulant, of a definite food of a constant composition and the determination of the subject's response to this normal stimulus. However, one of the earliest and most constant symptoms of a lack of vitamin B is anorexia. Therefore, it is impossible to use a voluntary consumption of food as a stimulus in this study. It is also difficult to devise a liquid test meal adequate in all respects except for the vitamin B complex which is suitable for administration by stomach tube and capable of exciting a generous flow of juice. Subcutaneous injection of histamine, however, can be used as a test for gastric function with great facility. It has been shown that histamine does not promote the secretion of pepsin, although it does stimulate the flow of water and hydrochloric acid (Gilman and Cowgill²² and Vineberg and Babkin²³). Therefore, when using this drug one is observing the basal and unstimulated secretion of enzymes. Even such an observation is significant. If the basal activity of the chief cells is unaffected by the deficiency in vitamin B, one might consider these cells capable of normal function. It is, of course, possible to take the view that the use of histamine is contraindicated on the ground that it is so powerful a stimulus—that observation of the production of an acid gastric juice in response to injection of histamine cannot be taken as indicating that the glands would show a similar response to the weaker, but more physiologic, stimulus such as results from the consumption of food.

Samples of gastric secretion were analyzed for pepsin by the Gilman and Cowgill²⁴ method, for free and combined hydrochloric acid by titration with fiftieth-normal sodium hydroxide using Topfer's reagent and phenolphthalein, respectively, as indicators, and for total chlorides by the method of Van Slyke (1923). Neutral chloride was estimated from the difference between acid and total chloride.

In experiments of the nature described it is important to determine the constancy of the response of the gastric glands to the same stimulus. This was accomplished by repeated tests with the same dose

22. Gilman, A., and Cowgill, G. R.: The Effect of Histamine upon the Secretion of Gastric Pepsin, *Am. J. Physiol.* **97**:124, 1931.

23. Vineberg, A. M., and Babkin, B. P.: Histamine and Pilocarpin in Relation to Gastric Secretion, *Am. J. Physiol.* **97**:69, 1931.

24. Gilman, A., and Cowgill, G. R.: The Determination of Peptic Activity: An Examination and Application of the Gates Method of Proteolytic Enzyme Titration, *J. Biol. Chem.* **88**:743, 1930.

of histamine on each animal during the preliminary period of subsistence on the adequate diet. These observations were made at least three weeks subsequent to the pouch operation, and after the animal had become completely accustomed to the routine of the experiment. Only after a sufficient number of these tests had been performed, so that the characteristic response of the completely nourished animal was established and easily recognized, was the daily supplementation of the diet with vitavose discontinued.

Results.—Since the results yielded by the different animals varied appreciably, pertinent data obtained from each dog are given. In order to show the kind of data secured in each experiment, an illustrative protocol (table 1) is presented.

TABLE 1.—Protocol of Experiment with Dog Petunia, May 8, 1930 *

Time, Min.	Rate of Secre- tion, Cc. per Hour	Concentration of Chlorine			Pepsin		Mucous†
		Acid, Milli- equivalents	Total, Milli- equivalents	Neutral, Milli- equivalents	Concen- tration,‡ Units per Cc.	Total Output, Units per Hour	
30	6.0	124.0	153.0	34.0	17,520	105,120	3
3 Mg. of Histamine Chloride Injected Subcutaneously							
15	21.2	135.2	156.0	20.8	11,040	242,000	2
30	43.2	153.0	168.8	10.8	3,666	153,400	1
45	45.2	159.2	168.0	9.8	1,660	48,180	0
60	16.0	157.2	168.8	11.6	5,080	81,280	1
75	2.6	141.0	159.0	18.0	16,000	41,600	1

* The dog was subsisting on an adequate diet and was in excellent condition.

† One per cent solution of a 1:10,000 dilution of commercial pepsin is taken as equal to 1,000 units, as described by Gilman and Cowgill.²⁴

‡ The amount present was estimated by the naked eye, and the results were expressed in terms of a scale of from zero to 3.

DOG "PETUNIA".—*Pavlov Pouch.*—This animal possessed a large pouch and thus produced a large volume of secretion. Observations were made over a preliminary period of about two months, during which time the volume and acidity of the gastric juice secreted in response to a constant dose of histamine varied but slightly. A protocol representative of one of these experiments is given in table 1.

The data presented in table 2 indicate roughly the constancy of the secretion so far as the volume of juice elaborated is concerned. The recorded rate of secretion is the maximum observed, occurring almost without exception forty-five minutes subsequent to the administration of the histamine. The rate of secretion in response to a given dose of histamine showed no appreciable change over a period of two months.

On July 15, the vitavose was removed from the diet and similar observations continued. On the eighteenth day of subsistence on the diet deficient in vitamin B (protocol, August 1) the maximum rate of secretion had fallen to 20.4 cc. per hour. On the twenty-first day the animal exhibited the characteristic anorexia. On the twenty-third and thirty-second days the maximum rates observed were 25.6 and 17.2 cc. per hour, respectively. The chemical composition of these samples was normal with respect to the variables under observation.

On the thirty-seventh day (August 20) a subcutaneous injection of histamine failed to produce gastric secretion. This experiment is of such interest that it is worth while to summarize it in detail. For thirty minutes the basal secretion of the stomach during fasting was collected. During that time the gastric glands produced only a very few drops of a thick viscous material. The animal was then given an injection of the usual dose of histamine. During the thirty minutes subsequent to this injection, the gastric secretion remained unchanged. At this point a second administration of histamine was superimposed on the first, with no effect on the gastric secretion. In order to make certain of the efficacy of the histamine employed, a fresh solution of the drug was made and injected in the dosage previously used. The dog was observed for another hour, during which time there was no secretion of a fluid gastric juice; only a fraction of a cubic centimeter of thick viscous product was collected. On analysis this material proved to be neutral in reaction. However, on extraction with acid it was demonstrated to possess an appreciable proteolytic activity.

No therapy was given the animal at this time, because it was considered desirable to repeat the foregoing experiment. On the following day (August 21), the animal was again subjected to the same experimental procedure, with identical

TABLE 2.—*Constancy in the Response of Dog Petunia to Injection of the Same Dose of Histamine Over a Period of About Two Months*

Date	Maximum Rate of Secretion, Cc. per Hour
May 8	45 0
May 10	44 8
May 13	46 0
May 15	37 2
May 19	45 6
May 21	42 4
July 2	39 0
July 15	40.4

results. After this trial the dog was given 50 Gm. of vitavose. A partial restoration of appetite was observed. Twenty-four hours after the administration of the vitamin the gastric secretory activity was again tested. The pouch, which during the previous few days had not contained any fluid, was partially filled with an acid juice. Stimulation with histamine produced a fairly generous flow of fluid, the maximum rate of secretion being 16.4 cc. per hour. Vitamin was again administered, and twenty-four hours later the rate of secretion had increased to 28.4 cc. per hour. The proteolytic activity of this secretion was within normal limits; however, the concentration of chloride was slightly lower than that usually observed.

A discussion of these results will be reserved until the data representative of the other experimental subjects have been presented. The fact to be kept in mind at this point, however, is that in the experiment just described, the dog at no time showed any of the symptoms of advanced deficiency in vitamin B, such as the neuromuscular manifestations.

DOG "BROWNIE".—*Pavlov Pouch*.—This dog, when tested from time to time, showed a fairly characteristic response to histamine. Four observations made on the animal, subsisting on the adequate diet, gave maximum rates of secretion of 22.4, 26.8, 24.4 and 26.4 cc. per hour. On the twenty-fourth day of the deficiency regimen the observed rate of secretion was 24.4 cc per hour. The rate of secretion was still unaffected on the fiftieth day. The significantly low rate of 18.8 cc. per hour was exhibited on the fifty-seventh day. Symptoms of advanced vitamin

deficiency appeared on the seventy-seventh day. These were not severe, being confined to the hindlegs. The response to histamine at this time was definitely reduced, the maximum rate of secretion being only 10 cc. per hour. Furthermore, the period during which the stimulus was effective was shorter than that usually observed. The chemical composition of the gastric juice secreted under these conditions was not abnormal. The acidity and total chloride values were slightly low but not significantly so. The samples were just as rich, if not richer, in pepsin than those previously observed.

Vitamin therapy brought about a rapid disappearance of the nervous symptoms. The response of the gastric glands to histamine was also greatly changed. Twenty-four hours after the administration of vitamin the volume rate of flow of the gastric juice had increased to 18.8 cc. per hour. After seventy-two hours it had reached its normal value (30 cc. per hour). This dog was observed for more than a year subsequent to the completion of the experiment just described, during which period it subsisted on an adequate diet. During this time the rate of secretion was always quite constant and characteristic, the maximum averaging around 28 cc. per hour.

Dog "Bozo."—*Pavlov Pouch*.—Four preliminary observations on this animal yielded the characteristic normal rates of secretion in response to a constant stimulus with histamine of 17.2, 13.6, 13.2 and 13.5 cc. per hour. The dog was then placed on the diet deficient in vitamin B and exhibited anorexia after a period of only thirteen days. Other observations made in our laboratory suggest that this animal may have had a poorer utilization of ingested vitamin or else a greater loss of this dietary factor through excretory channels. On the thirty-third day of the deficiency regimen the rate of secretion had fallen to 6.8 cc. per hour. On the fortieth day very severe and typical symptoms of deficiency in vitamin B (B_1) developed. The rate of secretion at this time was 6.4 cc. per hour. Vitamin B therapy was followed within forty-eight hours by a maximum gastric response to histamine of 12.8 cc. per hour, which was very close to the previously observed normal value. The acid and pepsin contents of this juice were normal.

Dog "Dolores."—*Heidenhain Pouch*.—The results obtained from this animal may be summarized briefly. This dog, with few exceptions, gave a constant and characteristic response to histamine. The picture exhibited during subsistence on the diet deficient in vitamin B was also classic, anorexia appearing on the twelfth day and definite neuritic symptoms on the seventy-fourth day. However, even coincident with the onset of the neuromuscular manifestations, the gastric secretion remained unchanged with respect to both the volume of juice secreted and its contents of acid and pepsin.

Comment.—The results summarized are varied. In three of the four dogs there was definite evidence of a diminished response of the gastric glands to stimulation with histamine during the state of deficiency in vitamin B. If the lack of antineuritic vitamin is the etiologic agent causing this altered gastric response, how can one explain the fact that the animal Petunia, the secretion of which was most markedly affected, showed no symptoms of a deficiency of vitamin B other than anorexia? On the other hand, Dolores, which exhibited advanced symptoms of neuritis, gave no evidence of a diminished gastric activity. Yet it is strongly indicated that the lack of vitamin is the essential remote, if not immediate, cause of the diminished secretion, because as a result of administration of the vitamin the function of the gastric

gland was rapidly restored to normal in the three animals which exhibited this disturbance. It is difficult to reconcile these facts. In view of the observations of Rose, Stucky and Cowgill,¹⁰ published since these experiments were performed, that a variable degree of anhydremia develops in deficiency of vitamin B, one might believe that the differences here noted are reflections of such a condition. The protocols of all the experiments were therefore examined from this point of view. The numerous data, omitted owing to lack of space, indicate clearly that one cannot attribute the changes in gastric response exhibited by these dogs to an accompanying anhydremia.

The fact that the three dogs possessing Pavlov pouches evidenced a diminished secretion, whereas the animal possessing a Heidenhain pouch remained normal so far as the gastric response is concerned, seems to be significant. The essential difference between these two types of pouches is that in the former the vagal nerve connections are intact, whereas in the latter the pouch has lost its primary vagal communication. However, one is at a loss to explain the observed results from such a consideration. In deficiency of vitamin B, the symptoms observed are characteristic of a hyperactivity rather than a hypo-activity of the nerves. A hypersensitivity of the vagus should lead to an increased rather than a decreased gastric secretion (Babkin²⁵). In these studies, however, all the dogs with Pavlov pouches exhibited a diminished function of the gastric glands.

There remained as a possible explanation of these results the fact that the experimental diet was deficient in both the B (B_1) and G (B_2) components of the vitamin B complex. The casein III diet which was fed to these dogs is practically devoid of vitamin B. It is true that the commercial casein used in its preparation contains a slight amount of vitamin G (B_2). Could it be possible that the gastric symptoms observed were manifestations of a varying degree of deficiency of the last-named component of the vitamin B complex? Experiments were therefore undertaken to test this hypothesis.

II. THE EFFECT OF SUBSISTENCE OF DOGS WITH GASTRIC POUCHES ON THE GOLDBERGER DIET 195 ON THE SECRETION AND CHEMICAL COMPOSITION OF GASTRIC JUICE

At the time these experiments were undertaken no one had successfully fed dogs over long periods on purely artificial diets adequate except with respect to vitamin G (B_2). The experience of one of us (G. R. C.) had indicated that in all probability this constituted a separate problem, and until it had been investigated with success, it seemed unwise to begin such an experiment with dogs with gastric pouches.

25. Babkin, B. P.: Vagal and Sympathetic Control of Gastric Secretory Functions, *Tr. Am. Gastro-Enterol. A.*, to be published.

Goldberger and his associates,²⁶ however, fed dogs certain food mixtures and observed the appearance of the canine disease called black tongue, which was believed to be the analog of pellagra in man and to be due chiefly, if not solely, to lack of vitamin G (B₂). It is quite likely, in view of more recent developments,²⁷ that these ideas of Goldberger and his co-workers require some modification. Since subsistence of dogs on the Goldberger 195 diet results in quite prompt production of a characteristic syndrome, it was believed that trials of this diet with our dogs with gastric pouches might enable us to determine the rôle, if any, of deficiency in vitamin G in bringing about changes in gastric response.

Experimental Data.—The experimental procedure in these studies was the same as that described in part I, with the exception of the diet employed. After the characteristic response of the dog subsisting on an adequate diet had been determined, the animal was given the Goldberger diet 195, and the observations were continued until manifestations of black tongue appeared, and therapy had been instituted. Four dogs were studied. Two of these animals had already been observed in the previous study. Thus dog Dolores, having shown no signs of gastric disturbance when subsisting on casein III ration, was realimented and then given the Goldberger diet. Dog Bozo, having shown a lessened gastric secretion when on the casein III diet, after realimentation was similarly given the black tongue-producing ration. In addition, two other dogs were included. In this study, therefore, there were two dogs with Pavlov pouches and two animals with Heidenhain pouches.

Results.—In view of the variations noted, it will facilitate proper understanding of the results if pertinent data for each animal are presented separately.

DOG "DOLORES."—*Heidenhain Pouch.*—This animal, while subsisting on the Goldberger diet, continued to secrete gastric juice in a normal fashion. After fourteen days on this ration a cage sore began to develop on the right hindleg over the protuberance of the proximal extremity of the femur. Before the completion of the experiment this sore had grown to tremendous proportions. In addition, symmetrically placed lesions of the skin appeared on each side of the head at the angle of the mandible and over the superciliary arches of the frontal bone. Lesions also appeared over the thorax, extending from the fifth to the seventh intercostal spaces. These were also symmetrically placed. Additional lesions were also noted over each clavicle.

26. Goldberger, J., and Wheeler, G. A.: Experimental Black Tongue of Dogs and Its Relation to Pellagra, Pub. Health Rep. **43**:172, 1928. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: A Further Study of Experimental Black Tongue, with Special Reference to the Black Tongue Preventive in Yeast, *ibid.* **43**:657 and 663, 1928.

27. For recent reviews relating to this topic see Sure, B.: The Present Status of Vitamin B₂ (G), J. A. M. A. **99**:26 (July 2) 1932, and Underhill, F. P.: Clinical Aspects of Vitamin G Deficiency, *ibid.* **99**:120 (July 9) 1932.

The dog's appetite over the first sixty days of the experiment was good, during which time she maintained her body weight. From the sixtieth to the seventy-eighth day the intake of food was erratic; the animal became rapidly weaker, and on the seventy-eighth day she refused all of the food offered. At this time the dog was most apathetic. A test of the stomach, however, revealed normal glandular response to histamine. Daily administrations of yeast were made in an attempt to save the dog's life. In spite of this therapy the animal died eighty-two days after the beginning of the experiment. It is interesting that at no time did this animal show any of the oral or intestinal lesions that have been described by Goldberger and attributed to deficiency in vitamin G (B_2).

DOG "ROBERTA."—*Pavlov Pouch*.—This dog had been observed over a period of eight months preceding the experiment to be described. During this period repeated tests showed her gastric secretory response to have been remarkably constant. The septum separating the gastric pouch from the main stomach was perforated. However, careful drainage permitted the quantitative evacuation of the contents of the pouch without contamination by material from the main stomach. The dog consumed the Goldberger diet ravenously and maintained a constant body weight. This continued for eighty-one days, during which time the secretion remained perfectly normal. On the eighty-first day the animal refused all the food offered. A test of gastric function was made on the eighty-sixth day. At this time the animal was regurgitating so much of the intestinal secretions that it was impossible to collect pure gastric juice because of contamination of the contents of the pouch through the perforated septum. However, a large volume of fluid containing free acid was obtained. The presence of free acid is significant because of the fact that the juice was contaminated with bile and doubtless alkaline pancreatic fluid. That one was able to obtain a sample of acid gastric secretion under such conditions indicates that the parietal cells were functioning in a capable manner. On the eighty-ninth day the characteristic lesions of the mouth developed, accompanied by profuse salivation, as described by Goldberger and his associates²⁶ and Underhill and Mendel.²⁸ A test of the gastric function made at this time revealed normal secretion. Fifty grams of whole yeast was administered by stomach tube. Twenty-four hours later no relief of the symptoms was evident. An additional 50 Gm. of whole yeast was given. On the following day the dog was found dead. Autopsy revealed diffuse hemorrhage in both lungs. It is believed that the primary cause of death of this animal was pneumonia, the development of which was probably facilitated by prolonged subsistence on the faulty diet.

One interesting lesion exhibited by this animal, which developed after sixty days of subsistence on the deficient diet, was loss of hair from the tip of the tail. The influence of the injection of histamine on this lesion was striking. When it first developed, the administration of histamine so affected the permeability of the capillaries at the tip of the tail that transudate would cross the capillary wall, as evidenced by the appearance of droplets on the exposed skin. The volume of this transudate was sufficiently great to cause a steady dripping from the end of the tail. After two weeks, however, these caudal capillaries apparently had lost their function to such an extent that the administration of histamine failed to produce any increased permeability, as evidenced by the fact that the exposed tissue remained perfectly dry.

28. Underhill, F. P., and Mendel, L. B.: A Dietary Deficiency Canine Disease: Further Experiments on the Diseased Condition in Dogs Described as Pellagra-Like by Chittenden and Underhill and Possibly Related to So-Called Black Tongue, *Am. J. Physiol.* **83**:589, 1928.

DOG "Bozo."—*Pavlov Pouch*.—It will be recalled that this dog showed a definitely diminished gastric secretion when subsisting on the diet deficient in vitamin B (B_1). In the present experiment there was no evidence of abnormality in this respect on the hundredth day of subsistence on the Goldberger diet. The experiment was terminated on the hundred and twelfth day.

DOG "ETHYL."—*Heidenhain Pouch*.—This animal became a coprophagist. Since the results obtained from the dogs already cited had been negative, no effort was made to keep this dog from access to her feces. It was deemed of interest to determine whether ingestion of the stools would protect the animal in view of the inadequacies of the diet. This proved to be the case for one hundred and four days, at which time observations were discontinued. The general condition was excellent, the appetite was good, and the dog gained weight during the course of the experiment. Her gastric response was normal.

Comment.—The results cited may be summarized as follows: Dogs subsisting on the Goldberger diet 195 show no loss of gastric function, as evidenced by the response of the gastric glands to a constant stimulation by histamine. Dogs Dolores and Roberta, even when evidencing terminal lethal symptoms considered to be the result of a dietary deficiency, showed normal gastric function. Dog Bozo, after one hundred and twelve days on the Goldberger diet presumably deficient in vitamin G (B_2), continued to secrete normally. On the other hand, after thirty-eight days' subsistence on the casein III ration, which was markedly low in antineuritic vitamin B and which probably contained more vitamin G (B_2) than the Goldberger ration, this dog showed a diminished secretion.

The conclusion to be drawn seems to be that the decreased gastric activity exhibited by three of the four dogs maintained on a diet deficient in the vitamin B complex (part I) was due to a lack of the B (B_1) substance. Administration of this factor rapidly restored the gastric secretory response to normal. Subsistence on the Goldberger diet did not affect the gastric response. However, in view of the uncertainties as to the exact nature of the inadequacies of the Goldberger ration, this study should be repeated, if possible, with a purely artificial diet adequate except with respect to vitamin G (B_2) before this dietary essential can be definitely ruled out as an etiologic factor in producing altered gastric function.

It is doubtful whether one can definitely relate the nervous symptoms so characteristic of lack of the vitamin B complex to a decrease in gastric activity. Dog Dolores continued to secrete in a normal manner and yet severe nervous symptoms developed. On the other hand, dog Petunia, in spite of the fact that she exhibited a complete and true achlorhydria, showed no nervous symptoms. The possibility exists that, even though the gastric response to histamine remained normal, the response of the acid-secreting glands to the less powerful stimulant of food may have been appreciably diminished. Such speculation is supported by the fact that while the experimental diet was used it was unnec-

essary to protect the abdominal muscles surrounding the opening of the pouch from the corrosive action of the escaping gastric juice. The amount of juice escaping was either too small in amount or insufficiently active to produce extensive proteolysis. The fact that actual tests of the gastric juice revealed normal content of pepsin suggests that its diminished hydrolytic power was due to a decrease in the amount of acid secreted. However, it is extremely doubtful whether the glands are inactivated to such an extent that the normal secretion is entirely devoid of hydrochloric acid. It was always possible to demonstrate the presence of free acid in the secretion of dog Dolores without offering such a powerful stimulant as histamine. It is most probable that the gastric glands are capable of producing an acid secretion, although the volume of this secretion is diminished. It is not likely, therefore, that the terminal syndrome characteristic of a deficiency in vitamin B (B_1) is of gastric origin.

SUMMARY AND CONCLUSIONS

The ability of dogs possessing gastric pouches to secrete gastric juice in response to a constant stimulus with histamine during the period of subsistence on a diet lacking the vitamin B complex was studied. The gastric juice was examined for acid and for proteolytic power. Of four dogs fed on artificial diet markedly deficient in vitamin B (B_1), in one a true achlorhydria developed, two evidenced a markedly diminished response to histamine, and one continued to show a normal response; the first three of these animals possessed Pavlov pouches and the fourth dog, a Heidenhain pouch.

Under the assumptions that the variations exhibited by these animals might have been due to varying degrees of a lack of vitamin G (B_2), and that the most outstanding deficiency of the Goldberger 195 diet is with respect to this vitamin, four dogs (two with Pavlov and two with Heidenhain pouches) were fed the Goldberger ration. In two of this group the symptoms described by Goldberger and his co-workers developed without showing any evidence of a loss of gastric function. Coprophagy on the part of a third animal operated to protect the dog against the appearance of such symptoms over a period of one hundred and four days; the fourth dog continued normal for one hundred and twelve days.

The indications of this study are that so far as any diminution of gastric secretion occurs during a regimen of lack of the vitamin B complex, this is due to the absence of the B (B_1) component. However, before it can be definitely stated that the G (B_2) factor plays no etiologic rôle with respect to such altered gastric secretory function, similar experiments should be performed on dogs subsisting on purely artificial diets which lack only vitamin G (B_2).

THE BLOOD IN NORMAL PREGNANCY

I. BLOOD AND PLASMA VOLUMES

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A tremendous number of data on physiochemical changes in the blood during pregnancy have been published, but, with one or two exceptions, the observations reported are based on groups of patients at different periods and not on the same patient throughout pregnancy and the puerperium. Realizing that the normal must be known before abnormalities can be detected, we began, three years ago, a systematic study of the blood of a number of women early in pregnancy and followed them into the puerperium. We also took a number of patients at term and followed them for eight weeks, or longer, after delivery. The reason for the latter series was the impossibility of getting patients before the tenth week of pregnancy, when there had already been some change in the blood, and, furthermore, the difficulty in persuading patients to submit to repeated studies, both before and after delivery, not to mention the possibility of harm to the patient from the procedures used.

Many reports on the volume of blood in pregnancy have been published, and, although the results are conflicting, the belief is prevalent that there is a considerable increase in the blood volume in pregnancy and that, because of this plethora, the pregnant woman can withstand a huge loss of blood at delivery without danger. In a careful review of the literature, we have not been able to find any data which absolutely demonstrate an increase, but we have found a marked lack of uniformity in the reports. Our interest in this subject is based on the following considerations: 1. Is there a sufficient increase in blood volume in pregnancy, as is frequently stated, to permit a loss of from 1,000 to 1,500 cc. of blood at delivery, with no obvious ill effect? 2. The estimations of the blood and plasma volumes form the basis for

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the determination of total hemoglobin, erythrocyte mass, serum protein, fibrin, total base, etc., which will be reported in subsequent studies.

3. If the blood and plasma volumes are increased, it is a phenomenon well worth study in itself.

DeLee¹ stated:

The total quantity of blood is augmented, especially in the last months, a true plethora existing (Kaboth and Zuntz), a fact proved by Miller by means of the "vital red" method, the volume being between 6 and 9 per cent of the body weight (Bohnen, 7-7.3 per cent), the gain being from 400 to 500 Gm. The need for more blood must be admitted; the addition of the fetus and the fetal circulation, the development of the uterine arteries and veins, the enlargement of the veins of the lower extremities, which are sometimes so great that they appear to be veritable caverns. It would seem that they act as reservoirs and provide for the loss of blood at labor. The veins collapse afterward, but never completely or permanently. This surplusage of blood should not beguile the accoucheur to wastefulness of the vital fluid during delivery.

Williams² stated:

Observations made in my clinic, in 1915, by Miller, Keith and Rowntree seem to show that during pregnancy there is a definite increase in both the plasma and blood volume, which disappears during the puerperium. These conclusions were based upon the injection of known quantities of "vital red" into the circulation, and the colorimetric comparison of the patients' serum with standard preparations of serum colored with the same dye. More extended, but as yet unpublished, observations by Harris in our service during 1922 and 1923 demonstrate that the volume of blood is definitely increased.

Kehrer³ reviewed the literature up to 1923 and concluded that during the second half and especially during the last two months of pregnancy a marked increase in the blood volume occurs, "a plethora of pregnancy." He stated that in the nonpregnant woman the blood volume ranged from 5 to 6.3 per cent of the body weight, but in pregnancy the range was from 7 to 8.3 per cent.

Denecke⁴ reviewed the German literature to 1923, and concluded that the blood volume is increased during pregnancy both in animals and in man (Spiegelberg and Gescheidler⁵ found, with Welker's method, that in dogs the blood volume increased from the normal of 7.87 per cent of the body weight to 10.5 per cent in the last half of pregnancy).

1. DeLee, J. B.: Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Company, 1928, p. 105.

2. Williams, J. W.: Obstetrics, New York, D. Appleton and Company, ed. 6, 1930, p. 207.

3. Kehrer, E., in Halban, J., and Seitz, L.: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1925, vol. 6, p. 783.

4. Denecke, G., in Hinselmann, H.: Die Eklampsie, Bonn, Friedrich Cohen, 1924, p. 294.

5. Spiegelberg, O., and Gescheidler, R.: Arch. f. Gynäk. 4:112, 1872.

Miller, Keith and Rowntree⁶ found that normally the amount of blood in cubic centimeters per kilogram ranged from 80 to 91, with an average of 84 cc., but in pregnancy at term the range was from 67 to 115 cc., with an average of 96 cc. The volume plasma varied normally from 48 to 56, with an average of 51 cc. per kilogram, but in pregnancy at term the range was from 38 to 73, with an average of 54 cc. per kilogram. Rowntree and Brown,⁷ in their discussion of this work, stated:

Following delivery there was a large decrease in the absolute blood volume, which was greater than could be accounted for by loss of blood at parturition. The average decrease in blood 7 to 10 days after delivery was 1,100 cc., whereas the average loss of blood at delivery was 300 cc. An increase in the total volume of the blood would be expected in pregnancy because of the fetal circulation. The fact that there is a decrease in the amount of blood following pregnancy in excess of the amount lost by hemorrhage would seem logical on the basis of Lucas and Deering's⁸ studies. They found that the volume of blood in the new-born infant varied from 330 to 850 cc. This amount is taken from the maternal circulation. The fetal blood and the amount of blood lost by hemorrhage would account for the difference in blood volume between pregnant and parturient women. This difference was disclosed by Keith and his associates. This study lends confirmation to the belief held in the early part of the nineteenth century that there is a plethora of pregnancy, and confirms the well known clinical observation of the relatively slight danger of loss of blood in the pregnant woman. In absence of data relating to transportation of dye from maternal to fetal blood, a word of caution in the interpretation of such data is necessary. It is possible that pre-edematous states of tissue may be concerned.

Their explanation of the average decrease of 1,100 cc. after delivery is incorrect in part, because (1) there is *no* direct connection between fetal and maternal circulations, and (2) the dye does not go through to the fetus. Therefore, any increase in blood or plasma volume found in pregnancy with a dye method is not due to the fetal circulation.

Schoenholz,⁹ in 1929, published an article on the volume of circulating blood in pregnancy, which is based on the largest series of patients so far reported. He identifies his cases by their initials and groups them in a number of tables in which the initials recur repeatedly, so that it is difficult to determine exactly how many patients were studied, and how many determinations were made on each. Approximately forty women were studied, but none earlier than the seventh month.

6. Miller, J. R.; Keith, N. M., and Rowntree, L. G.: Plasma and Blood Volume in Pregnancy, *J. A. M. A.* **65**:779 (Aug. 28) 1915.

7. Rowntree, L. G., and Brown, G. E.: *The Volume of the Blood and Plasma*, Philadelphia, W. B. Saunders Company, 1929.

8. Lucas, W., and Deering, B.: Blood Volume in Infants Estimated by the Vital Dye Method, *Am. J. Dis. Child.* **21**:96 (Jan.) 1921.

9. Schoenholz, L.: *Arch. f. Gynäk.* **138**:596, 1929.

Seventeen patients had three antepartum determinations—all after the seventh month—and one postpartum determination on the sixth to the tenth day. These all showed an average antepartum increase of 2.7 per cent. Eight patients similarly studied did not show change in blood volume. He also determined the blood volumes in nine patients, using both carbon monoxide and trypan red, and made the following conclusions: (1) With these methods only the volume of circulating blood and not the total volume of blood is determined; and (2) the former is not a constant, but is dependent on external influences, i. e., temperature and exercise. The colorimetric method deals with the plasma, while the carbon monoxide method deals with the hemoglobin in the erythrocytes. The distribution of the erythrocytes and the plasma varies in the different parts of the vascular system. A comparison of the figures of different investigators has only limited value, but the significance of such investigations remains great in the hands of any one person.

In his figures, which compared with values of nonpregnant women do show a small increase in the volume of circulating blood during pregnancy, are included those for the susceptible circulating fetal blood.

As a result of its increased hemoglobin content, the fetal blood has a greater capacity for carbon monoxide than the maternal blood. In consequence, the value found for the maternal blood by this method is too high; therefore, the circulating blood volume calculated by the carbon-monoxide inhalation method, which is concerned with the hemoglobin, is certainly not appreciably increased at the end of pregnancy. However, an increase in the plasma volume may be found by the dye methods. The conclusion is to be drawn that a dilution of the blood occurs during pregnancy and from this the fact that pregnant women withstand blood loss better than non-pregnant women is self-explanatory.

In table 1 are listed data on blood volume, together with the method used. We have not included all of the determinations by different observers, but have selected those which were based on the largest series and which seemed representative. It is obvious that one can compare only results by the same method, but even with the same method different results are reported in pregnancy. A study of table 1, together with our collective review of the literature, shows that the problem of whether or not a change in the blood volume occurs in pregnancy is still unsettled. It has also been demonstrated both by us and by others that a standardized method will give results for blood and plasma volumes which will be fairly constant over a long period of time. The marked variations in pregnancy, reported by different investigators, are due, in part, to the fact that all results are based on the weight, which is extremely variable in pregnancy because of the many components which make up the increase (the fetus, placenta, amniotic fluid, increase in the size of the uterus and "physiologic

edema"¹⁰ of pregnancy, altogether amounting to from 7 to 10 or more kilograms). Therefore, to study changes in blood and plasma volume in pregnancy, one must follow the same patient throughout and draw conclusions from a study of the total volumes and not from calculations based on weight or on any function of the latter.

TABLE 1.—*Reported Values for Blood Volume in per Cent of Body Weight*

Authors	Method	Blood Volume, per Cent			Number of Cases
		Non-pregnant	Pregnancy at Term	Puerperal	
Plesch (Ztschr. f. exper. Path. u. Therap. 6: 380, 1909)	Carbon monoxide	4.7-6.1			
Zuntz (Zentralbl. f. Gynäk. 35: 1365, 1911)	Carbon monoxide	...	8.4	6.0	6
Schoenholz ⁹	Carbon monoxide	6.3	6.7	6.5	40±
Schoenholz ⁹	Trypan red	...	9.0	...	9
Fries (Ztschr. f. Geburtsh. u. Gynäk. 59: 340, 1911)	Antitoxin	7.9	7.4	8.7	10
Mahnert (Arch. f. Gynäk. 116: 168, 1921)	Refractometric	6.3	8.0	...	10
Gueissaz and Wanner (Schweiz. med. Wehnschr. 52: 1173 and 1216, 1922)	Refractometric	...	12-15% increase	...	12
Knauth (Zentralbl. f. Gynäk. 57: 498, 1923)	Congo red	6.2	6.8	...	20
Neubauer (Deutsche med. Wehnschr. 49: 520, 1923)	Congo red	6.8	7.4	6.2	8
Koch and Jakobovits (Klin. Wehnschr. 1: 2518, 1922)	Congo red	5.7	5.4	...	24
Bohnen and Boormann (Arch. f. Gynäk. 126: 144, 1925)	Congo red	6.4	7.6	...	20
Böttcher (Dissert., Freiburg; quoted by Schoenholz ⁹)	Trypan red	8.4	9.7	...	10
Hnátěk (Zentralbl. f. Gynäk. 51: 2328, 1927)	Trypan blue	7.8	9.4	8.6	
Rowntree and Brown ⁷	Vital red Congo red	Range, 80.2-91.3 Average, 84.2 cc. per Kg. Plasma Range, 47.8-56 Average, 50.5 cc. per Kg.			
Miller, Keith and Rowntree ⁸	Vital red	...	9.6% Range, 67-115 Average, 91 cc. per Kg. Plasma Range, 38.1-72.7 Average, 54.5 cc. per Kg.	...	13

We have not been able to find any work in which this was done, for all of the reports are based on a number of observations made on different women at the various periods of pregnancy and are calculated

10. Practically all pregnant women have an increased amount of body water, which is usually manifested late in pregnancy by one or more of the following: pitting edema of the lower extremities, excessive and rapid increase in weight, a marked diuresis (negative water balance) after delivery or death of the fetus, and—or—a marked loss of weight post partum.

on the weight, being reported either as percentage of body weight or as cubic centimeters per kilogram.

For a study such as we contemplated only two methods were adaptable: (1) the dye method, in which the plasma volume is determined, and (2) the carbon monoxide method, in which both the circulating hemoglobin and myohemoglobin are determined. The latter method was undesirable because it would include the fetal blood, and no correction could be made because of the varying hemoglobin and constantly changing oxygen capacity of this fetal blood. We, therefore, chose the dye method, realizing that no method will give the absolute plasma or blood volume, but believing that one can, with proper technic, obtain consistent results. In table 2 we give data on blood and plasma volumes, hematocrit readings etc., on ourselves. The small variations indicate that the blood volume is maintained within

TABLE 2.—*Repeated Determinations of Blood Volume on Normal Persons*

Name	Date	Weight, Kg.	Hemato- crit, per Cent	Blood			Plasma		
				Volume, Cc.	Cc. per Kg.	Cc. per Sq. M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq. M.
W. J. D.	1/22/31	87.7	50	5,752	65.5	2,930	2,876	32.8	1,460
	2/ 3/31	87.7	50	5,614	64.0	2,860	2,807	32.0	1,430
C. W.	1/22/31	59.0	46.3	4,350	73.8	2,650	2,349	39.8	1,440
	2/ 9/31	59.0	45.0	4,450	75.4	2,710	2,448	41.5	1,490
	12/24/32	59.0	44.0	4,571	77.5	2,780	2,560	43.3	1,560

narrow limits. The results of two determinations of plasma volume on nine normal men, by Keith, Rowntree and Geraghty,¹¹ showed an average variation between the two determinations of 1.5 per cent. Rowntree and Brown,⁷ in normal persons over a period of from two to fourteen days, reported an average variation of 5.8 per cent; whereas, over periods of from one to twenty-four months, the mean variation was 8.6 per cent. Therefore, changes in volume, to be significant, must be plus or minus 5 per cent. We have disregarded changes unless they were greater than 5 per cent.

We planned to obtain volumes on the same patient at monthly intervals throughout pregnancy, but found that certain women (six in number) were susceptible to the dye (vital red), in that the skin of the face, especially below the eyes, and of the arms and trunk was stained red (from three injections); the discoloration was still present nine weeks after delivery. Our plan was, therefore, modified, and three determinations were obtained ante partum and from one to three, post partum. Congo red was substituted for vital red, and in

11. Keith, N. M.; Rowntree, L. G., and Geraghty, J. F.: A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**:547 (Oct.) 1915.

over three hundred determinations no further difficulties have been encountered. We started with twenty-five patients, early in pregnancy, but have been able to follow completely through pregnancy and post partum only fifteen, designated as series A. Since practically all of our patients were seen first after the tenth week, we obtained determinations on other patients before delivery and also from three to eight weeks post partum, believing that at this time the blood and plasma volumes should be normal. The latter group is designated as series B. Our conclusions are based on the data obtained by repeated determinations of the blood volume on the same patient. Thus, we had twenty patients with two determinations, sixteen with three, eighteen with four, and four with five determinations.

METHOD

We used Keith and Rowntree's method, in which the plasma volume is determined by means of vital red, and the blood volume calculated from it. The method was first used as outlined by them, but we soon saw that a given amount of solution could be injected more accurately than varying amounts. Therefore, either 8 or 10 cc. of the dye, depending on the patient's weight, was injected. As an anticoagulant for determining cell volume, heparin was used. In the original method approximately twice the amount of dye used by us was injected, and the determination was made by diluting the plasma 1:4 and setting the colorimeter at 10. We injected only half the amount of dye, diluted 1:4, but set the colorimeter at 20. The results were identical, but the colorimetric error was considerably reduced. The syringes were standardized and were used for nothing else. The pipets used for the dilutions were certified, and the standard for each colorimeter determination was made from a portion of the same dye which had been injected. Most of the determinations were made with the patient lying on her back, but some were made in the sitting position. There was a period of rest of at least twenty minutes before the dye was injected. The complete determination of blood volume was always carried out by one of us; therefore, we were able to prevent the occurrence of hemolysis which would have made the determination valueless. A recent article by Graff and Clarke,¹² on studies in which the spectroscope was used to determine the presence of hemoglobin, is a valuable contribution, but with proper technic one can prevent the occurrence of hemolysis.

For purposes of comparison, volume figures must be reported on some basis, which may be weight, surface area, etc., but, as we have pointed out, with a variable weight the figures have no real significance. In tables 3 and 4 we have grouped our results on a basis of cubic centimeters of blood and plasma per kilogram of uncorrected body weight. The wide range from 53 to 113 cc. of blood per kilogram and from 32 to 71 cc. of plasma per kilogram shows definitely that changes in the amount of blood and plasma per kilogram have no significance when the

12. Graff, S., and Clarke, H. T.: Determination of Plasma Volume, *Arch. Int. Med.* 58:808 (Nov.) 1931.

weight is changing also. We have also made similar calculations on a corrected body weight (deducting a theoretical weight for fetus, amniotic fluid and placenta) and, likewise, the range is still great. The figures in the row marked "Total" designate the number of patients in the period of pregnancy shown who had the volumes per kilogram indicated, and

TABLE 3.—*Cubic Centimeters of Blood per Kilogram: Variations and Averages in Pregnancy and the Puerperium*

Cc. per Kg.	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	8-15	16-25	26-35	36-40	2-6	10-25	8 Wks.
50- 59.....	4	..	1	3	2	1	..
60- 69.....	5	1	5	9	7	11	2
70- 79.....	5	5	4	8	5	9	3
80- 89.....	4	1	12	25	6	6	6
90- 99.....	5	2	4	6	2	7	..
100-109.....	2	..	1	3	1	4	..
110-114.....	1	1	3	..
Total.....	25	9	27	55	24	41	11
Mean							
Total cases.....	77.3±2.1	79.5	80.4±1.6	80.9±1.2	77.0±2.0	82.1±1.9	
Standard deviation...	15.9		11.6	13.3	14.8	18.0	
Series A.....	76		76	76.4	75.3	84.4	
Series B.....	81.1	74.2	77.2	79.2

TABLE 4.—*Cubic Centimeters of Plasma per Kilogram: Variations and Averages in Pregnancy and the Puerperium*

Cc. per Kg.	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	8-15	16-25	26-35	36-40	2-6	10-25	8 Wks.
30-39.....	5	1	2	6	..	3	1
40-49.....	10	5	11	21	12	20	5
50-59.....	8	3	12	21	11	11	5
60-69.....	2	..	2	7	1	6	..
70-74.....	1	..
Total.....	25	9	27	55	24	41	11
Mean							
Total cases.....	47.3±1.2	47.5	49.7±1.0	49.8±0.8	49.9±0.8	50.1±1.1	
Standard deviation...	9.2		7.4	8.3	5.8	10.7	
Series A.....	45.4		47.2	47.2	46.6	50.2	
Series B.....	50.4	47.0	48.4	49.2

the means per kilogram are calculated for these different groups. The standard deviations and the difference between means for the various periods of the "total cases" have been calculated, and the latter figures indicate that the variations of the blood and plasma volumes per kilogram are of no significance.

The figures for both blood and plasma are lower than those reported by Miller and his co-workers. Series A shows no appreciable change ante partum, but a slight increase at from ten to fifteen days post partum, which is just the opposite of Miller's findings. These calculations are

based on weight and are, therefore, misleading because figures for total blood volume (table 6) indicate that there was no appreciable change in blood volume in five cases (the apparent increase was due to loss of weight incident to delivery), a decrease in five and an increase in three. Total plasma volumes showed that there was no change in two cases, a decrease in nine and an increase in two. With the general stimulus to metabolism and the maturing of the woman incident to pregnancy, one would expect that patients with low blood and plasma volumes before pregnancy would tend to retain a portion of the increase. Series B shows a marked drop at from ten to fifteen days post partum, with a return at eight weeks to a figure only slightly below that found in pregnancy. However, at eight weeks, only one of the patients had a total blood volume greater than the one obtained at term. All but two (no change)

TABLE 5.—*Range of Variations of Blood and Plasma Volumes*

Increase or Decrease, per Cent	Number of Patients Showing Increase Above Initial Determination				Number of Patients Showing Decrease Below Last Antepartum Determination							
	26-35 Weeks		36-40 Weeks		2-6 Days		10-15 Days		18-26 Days		8-17 Weeks	
	B.*	P.†	B.	P.	B.	P.	B.	P.	B.	P.	B.	P.
6-9	1	1	2	..	4	2	2	6	1
10-19	3	4	1	4	4	5	5	9	1	2	7	6
20-29	4	5	1	1	3	7	7	5	2	2	..	1
30-39	1	1	3	2	6	1	5	3
40-49	1	2	1	1	1
50-59	1	1	1
60-69	1	1
90	1
106	1

* B. = blood.

† P. = plasma.

of the total plasma volumes showed decreases. Thus, studies on the blood after delivery must be made after a longer interval than two weeks, if they are to be of value.

Table 5 shows the variations in blood and plasma volumes in percentage of increase and decrease, together with the number of cases showing the various changes. All antepartum values are divided by the first one obtained and the quotient multiplied by 100. Thus all data are converted to a common basis, and changes in different patients can then be compared. Postpartum values were converted similarly, but the determination at term was used as the divisor. In other words, the first antepartum volume is assumed to be 100 per cent, and the subsequent determinations are expressed in percentage of increase or decrease relative to it. Similarly, postpartum volumes are expressed in percentage of decrease or increase, relative to the determination at term, which is assumed to be 100 per cent. The cases showing variations of 5 per cent or less are classed as those with no appreciable change. These results

indicate that in the majority of cases there is a marked increase in blood and plasma volumes in pregnancy with a commensurate decrease after delivery. More cases showed larger increases in plasma volume than in blood volume. Increases in blood and plasma volumes of 30, 40, 60 per cent, etc., seem improbable and suggest that either a mistake was made in the determination or the patient had developed a tolerance for the dye. However, the increases in each patient were consistent; likewise, this same patient showed marked decreases post partum, thus demonstrating that the method was not at fault.

Table 6 gives essential data on series A, that is, on those patients who were followed throughout pregnancy and the puerperium. The pregnancy and puerperium were normal, unless the notes under "Comment" indicate otherwise. Changes in blood and plasma volumes, at least in these patients, had no effect on the labor, size of the baby, amount of milk or incidence of infection. The figures in column 2, which were derived by calculations similar to those described in the preceding paragraph, show the individual variations in blood and plasma volumes in per cent. The patients who had low volumes per kilogram (columns 3 and 7) when first seen usually had the greatest increase, and, as a rule, they tended to retain some of this excess blood and plasma after delivery, with the result that the volumes per kilogram were closer to the normal than were the first figures. This is shown best in patients 1, 5, 7 and 9. Three of the patients showed a decrease of blood of more than 1,000 cc. after delivery, but the majority showed either an increase or no change, thus differing from those of Miller and his co-workers. It is evident that in order to obtain consistent and significant results determinations must be made at a later date in the puerperium. The data on the amount of blood per square meter are included for completeness. Essentially, the same changes take place if the volumes are calculated on the surface area, as would be expected, because one of the factors used in calculating the surface area is the weight. Rowntree and Brown⁷ stated that pregnancy is characterized by a "simple hypervolemia" (increase in blood volume with a normal ratio of cell and plasma) which develops in the last month and lasts from two to three weeks post partum. Our data indicate that pregnancy is characterized by an "oligocythemmic hypervolemia" (increase in blood volume with a reduced number of cells—hematocrit figures are given in a subsequent paper), which develops as early as the beginning of the second trimester, reaches a maximum at term and fluctuates somewhat for the first three weeks after delivery, but the general trend is a return to the normal "simple normovolemia." The gains in blood and plasma shown by most patients are another indication of the profound changes produced by pregnancy in the maternal organism.

TABLE 6.—Data on Patients Followed Throughout Pregnancy and the Puerperium (Series "A")

Patient, Gravida, Race,* Age	Date	Period of Ges- tation or Post Partum	Com- ment: Loss of Blood at De- livery†	Wt., Kg.	Sur- face Area, Sq. M.	Blood				Plasma			
						Total Volume		Cc. per Kg.	Cc. per Sq. M.	Total Volume		Cc. per Kg.	Cc. per Sq. M.
						Change,				Change,			
						Cc.	%			Cc.	%		
						1	2	3	4	5	6	7	8
1 II W 20	1/ 7/31 4/22/31 8/ 3/31 8/14/31	13 wks. 29 wks. 40 wks. 12 days	200±	46.3 55.9 59.5 50.4	1.48 1.59 1.64 1.53	3,113 5,009 5,930 5,520	... 160 190 93	69 91 100 110	2,100 3,130 3,620 3,610	1,863 3,106 3,855 3,478	... 166 206 90	40 56 65 69	1,260 1,939 2,350 2,270
2 I W 23	2/25/31 5/ 7/31 8/20/31 9/ 1/31	14 wks. 30 wks. 40 wks. 12 days	200±	77.9 81.0 80.9 73.6	1.82 1.85 1.85 1.77	4,585 4,951 4,968 4,643	... 108 108 93	59 61 62 63	2,570 2,670 2,680 2,620	2,935 3,367 3,478 3,018	... 115 119 86	38 42 43 41	1,610 1,820 1,850 1,700
3 I W 23	1/14/31 5/13/31 6/27/31 7/ 7/31	15 wks. 30 wks. 40 wks. 12 days	200±	53.0 61.1 63.5 53.0	1.66 1.70 1.73 1.66	5,221 6,415 5,444 5,601	... 123 104 103	98 105 86 106	3,150 3,770 3,140 3,380	2,978 3,720 3,440 3,137	... 125 116 91	56 61 54 59	1,790 2,190 1,990 1,890
4 VII W 30	2/ 4/31 5/13/31 7/30/31 8/10/31	14 wks. 27 wks. 40 wks. 14 days	200±	92.2 91.7 87.0 82.7	2.07 2.07 1.99 1.95	5,369 6,318 7,143 5,750	... 118 133 81	58 69 82 70	2,600 3,050 3,680 2,940	3,007 3,669 4,000 2,990	... 122 133 75	53 40 46 36	1,450 1,770 2,010 1,530
5 II W 25	1/21/31 5/13/31 8/ 4/31 8/20/31	12 wks. 28 wks. 39 wks. 14 days	Cesarean section 200±	53.6 59.5 60.0 52.5	1.45 1.52 1.52 1.44	3,681 4,448 4,822 5,932	... 121 131 123	69 75 80 113	2,540 2,920 3,170 4,120	2,135 2,753 2,990 3,678	... 129 140 123	40 75 80 113	1,470 1,810 1,970 2,530
6 I W 19	2/24/31 5/26/31 8/25/31 9/ 4/31	14 wks. 27 wks. 40 wks. 11 days	200±	45.9 54.8 63.5 56.0	1.41 1.52 1.61 1.53	3,438 4,448 5,091 5,015	... 129 148 99	75 81 80 90	2,420 2,920 3,106 3,280	2,201 2,753 3,106 2,909	... 116 141 94	48 50 49 52	1,560 1,810 1,930 1,900
7 VI W 31	10/22/30 1/16/31 3/26/31 4/ 2/31 4/10/31	14 wks. 30 wks. 40 wks. 5 days 13 days	150 ml.	107.2 112.5 114.6 100.3 100.4	2.14 2.18 2.20 2.08 2.03	5,756 5,910 6,471 6,250 7,838	... 103 112 97 121	54 53 56 63 78	2,690 2,710 2,940 3,000 3,770	3,454 3,783 3,883 4,000 4,933	... 110 112 103 127	32 34 34 40 49	1,610 1,730 1,760 1,920 2,370
8 III C 30	12/ 4/30 3/11/31 4/30/31 6/ 8/31	14 wks. 28 wks. 40 wks. 11 days	200±	92.9 103.5 108.9 100.0	2.05 2.15 2.20 2.11	6,643 6,269 7,050 5,395	... 95 106 77	72 61 65 54	3,240 2,910 3,200 2,560	4,318 3,950 4,301 3,669	... 92 100 85	46 38 39 37	2,100 1,840 1,950 1,740
9 I C 21	10/29/30 2/18/31 4/13/31 4/15/31 4/24/31	14 wks. 29 wks. 40 wks. 3 days 12 days	200±	50.0 58.8 60.0 55.8 52.5	1.45 1.55 1.56 1.51 1.48	3,968 4,800 5,209 4,914 5,106	... 121 131 93 98	79 82 87 88 97	2,740 3,100 3,380 3,270 3,480	2,500 3,168 3,232 3,047 2,962	... 127 129 94 92	50 54 54 55 56	1,720 2,040 3,130 2,020 2,000
10 I W 26	9/ 2/30 9/23/30 12/ 4/30 12/13/30	20 wks. 23 wks. 36 wks. 3 days	200±	71.8 72.0 75.5 70.3		5,341 4,540 6,428 5,301		74 63 85 75		3,205 2,815 3,600 3,181		45 39 48 45	
11 I W 22	4/ 1/31 6/23/31 9/14/31 9/23/31	15 wks. 28 wks. 39 wks. 12 days	200±	67.2 73.8 76.5 68.1	1.70 1.76 1.79 1.71	5,830 5,763 5,763 6,107	... 99 99 107	87 78 75 91	3,420 3,270 3,220 3,600	3,440 3,516 3,516 3,298	... 102 102 94	51 48 46 43	2,020 2,000 1,970 1,930
12 I C 23	2/ 9/31 6/16/31 9/17/31 9/28/31	9 wks. 27 wks. 40 wks. 11 days	200±	61.3 80.0 86.3 75.6	1.69 1.90 1.95 1.85	5,213 6,783 4,901 4,961	... 130 94 101	85 85 57 66	3,080 3,570 2,510 2,680	3,076 4,102 3,137 3,076	... 133 102 97	50 51 36 41	1,820 2,160 1,610 1,660
13 VIII C 37	1/28/31 6/ 3/31 8/26/31 9/ 4/31	11 wks. 29 wks. 40 wks. 11 days	200±	63.1 75.4 71.5 65.6	1.78 1.85 1.81 1.74	6,168 6,046 5,574 5,686	... 93 90 102	91 80 78 87	3,460 3,270 3,060 3,270	3,578 3,809 3,555 3,298	... 106 99 93	52 50 50 50	2,000 2,060 1,960 1,890

* In this and the following table W indicates the white race; C, the colored race.

† In this and the following table the loss of blood at delivery, unless excessive or measured, is assumed to be approximately 200 cc.

Table 7 gives essential data on series B, comprising patients who were followed up to eight weeks post partum. The data have been arranged similarly to those in the preceding table. Up to three weeks post partum

TABLE 7.—Data on Patients Followed from Term to Eight Weeks Post Partum (Series "B")

Patient, Gravida, Race, Age	Date	Period of Gestation or Post Partum	Comment: Loss of Blood at Delivery	Weight, Kg.	Blood			Plasma		
					Total Volume		Cc. per Kg.	Total Volume		Cc. per Kg.
					Cc.	Change, %		Cc.	Change, %	
					1	2	3	4	5	6
I, C 15	10/13/31	39 wks.	200±	67.0	6,557	..	98	4,000	..	60
	10/27/31	12 days		56.5	4,418	67	80	2,563	64	45
	12/ 9/31	8 wks.		53.6	5,316	81	99	2,977	74	55
32 I W 27	9/22/31	40 wks.	1,020	65.0	5,555	..	85	3,333	..	51
	9/29/31	3 days		58.0	3,789	68	65	2,577	77	44
	10/ 8/31	12 days		55.5	4,284	77	77	2,742	82	49
	11/25/31	8 wks.		60.5	4,545	82	75	2,727	82	45
33 II W 29	11/ 5/31	40 wks.	75	103.4	5,701	..	55	3,877	..	38
	11/13/31	3 days		90.0	5,937	104	66	3,800	98	42
	11/29/31	19 days		87.5	5,396	95	62	3,454	89	40
	1/13/32	9 wks.		89.2	6,115	107	69	4,036	104	45
34 I C 25	12/18/31	40 wks.	550	72.2	6,000	..	83	3,600	..	50
	1/16/32	12 hrs.		64.7	4,161	..	64	2,622	..	41
	1/20/32	5 days		63.1	3,876	65	61	2,597	78	41
	3/10/32	8 wks.		64.5	5,193	87	80	3,168	88	49
35 II, W 24	9/ 9/31	36 wks.	400±	68.1	5,085	..	74	3,153	..	46
	10/11/31	11 days		61.5	4,089	80	66	2,781	83	45
	11/25/31	8 wks.		58.6	4,280	84	73	2,654	84	45
36 I C 25	9/20/31	40 wks.	200±	68.4	4,648	..	68	3,161	..	46
	(in labor)									
	9/23/31	3 days		63.0	4,700	101	75	3,479	110	55
	10/ 1/31	12 days		56.8	3,629	78	64	2,722	86	48
37 III, W 30	11/18/31	8 wks.	200±	54.5	4,453	96	82	3,162	100	58
	9/13/31	38 wks.		82.0	7,870	..	96	4,880	..	60
	9/26/31	12 days		73.0	4,786	61	65	2,920	60	40
	11/18/31	8 wks.		75.0	6,392	81	85	4,155	85	55
39 I, W 17	9/ 4/30	39 wks.	200±	67.5	5,610	..	83	3,254	..	48
	9/18/30	11 days		51.9	3,613	64	70	2,168	67	42
	1/31/31	17 wks.		50.0	3,181	57	64	1,909	59	38
40 III C 28	11/15/31	40 wks.	50	54.0	4,584	..	85	2,934	..	54
	11/18/31	3 days		43.2	4,867	106	101	2,823	96	59
	12/ 9/31	25 days		46.8	4,570	100	98	2,925	100	62
	1/12/32	8 wks.		47.2	3,853	85	82	2,408	82	51
43 I C 17	10/22/31	38 wks.	60	72.2	6,083	..	84	3,711	..	51
	Del. 27									
		5 days		63.5	4,875	80	77	2,633	71	41
	11/14/31	19 days		62.2	7,081	115	113	4,078	110	65
	12/22/31	8 wks.		61.9	5,120	84	83	3,175	86	51

the changes in blood and plasma volumes were variable, but at eight weeks almost all of the patients demonstrated a decided decrease in the total blood and plasma volumes; however, the volumes per kilogram either tended to remain constant or showed an increase toward the normal average.

Table 8 is arranged to show antepartum changes in the blood and plasma volumes. The calculations used are given in a previous paragraph (table 5). The table is detailed, and the data prove conclusively that there is an increase in blood and plasma volumes in pregnancy. This

TABLE 8.—Average Changes in Blood and Plasma Volume Calculated on Variations in Total Volume, Using the Initial Determination as One Hundred per Cent for the Antepartum Period

	Blood Volume		Plasma Volume	
	Number of Cases	Volume Change, per Cent	Number of Cases	Volume Change, per Cent
From 26 to 35 weeks' gestation:				
Average increase in all cases.....	17	15.8	17	18.2
Average increase in those showing increase..	11	27.4	13	26.0
Average decrease in those showing decrease..	2	14.0	3	10.0
No change in volume.....	4	0	1	0
From 36 to 40 weeks' gestation:				
Average increase in all cases.....	14	22.5	14	24.8
Average increase in those showing increase..	10	33.0	10	34.4
Average decrease in those showing decrease..	2	8.0
No change in volume.....	2	0	4	0

TABLE 9.—Average Changes in Blood and Plasma Volumes Calculated on Variations in Total Volume, Using the last Antepartum Determination as One Hundred per Cent for the Postpartum Period

	Blood Volume		Plasma Volume	
	Number of Cases	Volume Change, per Cent	Number of Cases	Volume Change, per Cent
From 2 to 6 days post partum				
Average decrease in all cases.....	24	13.5	24	11.0
Average decrease in those showing decrease..	17	20.6	14	20.5
Average increase in those showing increase...	2	14.5	2	15.5
No change in volume.....	5	0	8	0
From 10 to 25 days post partum				
Average decrease in all cases.....	40	10.2	40	10.0
Average decrease in those showing decrease..	23	22.0	28	18.5
Average increase in those showing increase...	7	14.8	6	19.8
No change in volume.....	10	0	6	0
From 8 to 17 weeks post partum				
Average decrease in all cases.....	10	15.6	10	15.6
Average decrease in those showing decrease..	8	19.9	8	20.0
Average increase in those showing increase...	1	7.0
No change in volume.....	1	0	2	0

increase is most marked in the last half of pregnancy, reaching a maximum at term. The increase in blood and plasma volume varies from 20 to 25 per cent.

Table 9 lists postpartum changes, and these data indicate that the decrease in blood and plasma volume after delivery is approximately the same as the antepartum increase; therefore, the conclusion that there is an increase in blood and plasma volumes at term is confirmed.

COMMENT

What is the need of an increase in blood and plasma volumes during pregnancy? Is it to fill the vessels of the uterus and lower extremities, as suggested by DeLee? If the latter is true, old multiparas, because of the increased number and size of the varicosities, should have larger volumes of blood and plasma than young primiparas; but this is not found. For example, patient 13, who was an octigravida, 37 years of age, with varicose veins, had the respective volumes given in table 4 and showed a decrease rather than an increase in blood volume at term. Patient 1 (gain of 90 per cent blood and 106 per cent plasma), patient 4 (gain of 33 per cent blood and plasma), patient 5 (gain of 31 per cent blood and 40 per cent plasma) and patient 46 (gain of 48 per cent blood and 41 per cent plasma) not only had no visible varicosities, but were in excellent physical condition and yet they experienced marked increases in volume. A possible explanation is that some increases in blood and plasma are necessary to supply the increase in maternal tissue (uterus and actual increase in weight incident to maturity, which is maintained after delivery), but the major portion is required to permit proper gaseous metabolism on the part of the fetus, involving as little extra work on the part of the mother as possible.

The fetal blood at birth has an oxygen capacity of 32 per cent by volume, but by the tenth day it has decreased to 23 per cent by volume (Peters and Van Slyke). This high capacity is necessary because the hemoglobin in the umbilical vein (arterial blood) is only 63 per cent saturated, whereas, normally, arterial hemoglobin is 95 per cent, and venous, 71 per cent saturated with oxygen. The blood in the placental sinuses is probably more like venous than arterial blood. Sufficient oxygen could be brought to the placenta, either by increasing the blood flow per minute, which would allow less time for gaseous diffusion, increasing the concentration of hemoglobin in the cell, or by increasing the number of erythrocytes. The latter would result in an increase in the viscosity of the blood and require more work by the heart. However, if both cells and plasma were increased proportionately, there would be no increase in viscosity, and gaseous exchange would be normal. The blood and plasma do increase, but the increase in plasma is greater, thus reducing the viscosity, and, as a result, the peripheral resistance may be diminished, thereby increasing the cardiac output. The result is that more blood is circulating, and more time is permitted for proper fetal respiration. Dreysel¹³ and Jagie¹⁴ found that the hearts of pregnant and puerperal women weighed more than those of normal

13. Dreysel, quoted by Williams.²

14. Jagie, N., in Halban, J., and Seitz, L.: *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenberg, 1926, vol. 5, p. 388.

persons, which, in view of the slight hypotension and normal heart rate found in this condition, would indicate an increased output of blood for each contraction. Stander and his co-workers¹⁵ have demonstrated both in dogs and in man that in pregnancy there is an increase in cardiac output, amounting to over 50 per cent of the normal value. Thus there is the mechanism to take care of an increased volume. It will be difficult to prove this theory, but in cardiac decompensation and severe anemia, cases in which the fetus would be most likely to suffer from an insufficient supply of oxygen, the fetal mortality is extremely high.

SUMMARY

The published reports on blood and plasma volumes in pregnancy are conflicting because they are based on the patient's weight, which not only is not constant, but is subject to marked variations in short intervals of time (fetus, placenta, amniotic fluid, increase in size of the uterus and physiologic edema of pregnancy, altogether amounting to from 7 to 10 Kg. or more). Furthermore, from 3 to 6 Kg. (fetus and amniotic fluid) of the increase has no direct connection with the maternal vascular system and would, therefore, have no influence in producing an increase in volume. Because of marked physiochemical changes in the blood in pregnancy, which are intimately associated with the well-being of the patient, it was thought important to determine definitely what the normal changes in blood and plasma volumes are in pregnancy. The same patient was followed throughout pregnancy and the puerperium, and the variations were calculated on total changes in volume. Determinations of blood and plasma volumes were made with a dye method (congo red) which, although it probably does not give the true value, does give consistent results with the proper technic. As the determination of percentage changes was the most important part of the study, the data reported are of significance.

The theory is advanced that the increase in blood and plasma volumes is a part of the mechanism by which gaseous exchange between mother and fetus is carried out with a minimal expenditure of work.

CONCLUSIONS

Previously reported values for blood and plasma volumes in pregnancy are at variance with each other, and the results are inconclusive because of the different methods used and the method of calculation. The volumes are reported either in cubic centimeters per kilogram or in percentage of body weight, either of which is unreliable because of the constantly changing weight in pregnancy.

15. Stander, H.; Duncan, E., and Sisson, W.: *Am. J. Obst. & Gynec.* **11**:44, 1926. Stander, H., and Cadden, J. F.: *ibid.* **24**:13, 1932.

Determinations of the blood and plasma volumes were made on various groups of women for the different periods of pregnancy. The cubic centimeters per kilogram and the means for the different periods were calculated, and although there is a slight increase at term, statistical analysis indicates that the changes are of no significance.

Similar studies in which the same women were followed throughout pregnancy and the puerperium indicate that the following changes occur :

1. The blood and plasma volumes begin to increase in the first trimester, and by the thirteenth week the gain amounts to 16 per cent and 18 per cent, respectively.

2. At term the average increase in the blood volume is 23 per cent and the plasma 25 per cent. This change is designated an "oligocythemichypervolemia." Although this increase seems large, losses of blood of 700 cc. or more are at once manifested in measurable reductions in volume. The pregnant woman survives losses of blood which would be fatal if she were not pregnant, partly because of the increase in blood volume, but more particularly because of the tremendous amount of fluid in her tissues.

3. At eight weeks post partum there is an average decrease of 16 per cent for both blood and plasma volumes. This does not quite equal the increase, but, since most of the patients weigh more after pregnancy, the discrepancy is explained.

4. The increase in blood and plasma volumes is not merely to fill vessels but is probably a part of the mechanism required to permit proper fetal respiration.

RHEUMATOID (ATROPHIC) ARTHRITIS

BACTERIOLOGIC CULTURES OF SYNOVIAL FLUID AND OF TISSUES

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During the past several years various attempts to isolate a micro-organism of etiologic significance from the synovial fluids, tissues or blood of patients with rheumatoid arthritis (atrophic, deforming arthritis) have yielded peculiarly inconsistent results. In the hands of most investigators a rather high percentage of cultures has remained sterile, while in the positive cultures a variety of micro-organisms have been obtained. While streptococci have most frequently been isolated by various groups of laboratory workers, other micro-organisms have also been obtained, and the results as a whole are not at all comparable as to either the kind or the number of organisms isolated. The one exception to this general statement is found in the reports of Gray and Gowen and of Gray, Fendrick and Gowen,¹ who repeated and confirmed the cultural work of Cecil, Nicholls and Stainsby, using a modification of the last author's technic.

Cecil, Nicholls and Stainsby² reported the frequent isolation of streptococci from the blood (in from 61.5 to 62.3 per cent) and joints (67.3 per cent) of patients with rheumatoid arthritis. The majority of these streptococci fell into a more or less homogeneous group, and were considered to be attenuated hemolytic forms. Gray and his co-workers reported the isolation of a streptococcus which "resembled the one Cecil considered specific for rheumatoid arthritis" in 62 per cent of their cultures from the blood or joints (61 per cent in their second report).

In contrast to the close approximation of these results, the majority of investigators—several of whom have attempted to carry out the technic described by Cecil, Nicholls and Stainsby—have recorded the isolation of a variety of organisms. Those most frequently reported

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1. Gray, J. W., and Gowen, C. H.: The Role of the Streptococcus in Arthritis Deformans, *Am. J. M. Sc.* **182**:682 (Nov.) 1931. Gray, J. W.; Fendrick, E., and Gowen, C. H.: Rheumatic Fever and Rheumatoid Arthritis from the Laboratory Point of View, *Texas State J. Med.* **28**:317 (Sept.) 1932.

2. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: The Bacteriology of Blood and Joints in Chronic Infectious Arthritis, *Arch.Int.Med.* **43**:571 (May) 1929; The Etiology of Rheumatoid Arthritis, *Am. J. M. Sc.* **181**:12 (Jan.) 1931.

have been hemolytic, indifferent or green-producing streptococci, staphylococci and diphtheroid bacilli.³ The positive cultures obtained usually represented a relatively small percentage of the total number of cultures attempted. The most consistent feature of these reports is the inconsistency of the results.

In the Hospital for Joint Diseases and its clinic, where patients presenting a large variety of conditions of the joints are under treatment, opportunity has been afforded of culturing synovial fluids and tissues, not only from cases of rheumatoid arthritis, but from cases of many other infectious and noninfectious conditions of the joints. The

3. (a) Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, *J. Bact.* **5**:511 (Sept.) 1920; Bacteremia Following Irritation of Foci of Infection, *J. A. M. A.* **99**:1496 (Oct. 29) 1932. (b) Billings, F.; Coleman, G. H., and Hibbs, W. G.: Chronic Infectious Arthritis. Statistical Report with End-Results, *J. A. M. A.* **78**:1097 (April 15) 1922. (c) Crowe, H. W.: Bacteriology and Surgery of Chronic Infectious Arthritis, New York, Oxford University Press, 1927. (d) Hadjopoulos, L. G., and Burbank, R.: A Preliminary Study Bearing on the Causative Factors of Multiple Infective Arthritis, *J. Bone & Joint Surg.* **9**:278 (April) 1927. (e) Forkner, C. E.; Shands, A. R., and Poston, M. A.: Synovial Fluid in Chronic Arthritis: Bacteriology and Cytology, *Arch. Int. Med.* **42**:675 (Nov.) 1928. (f) Poston, M. A.: Gland Cultures in Infectious Arthritis, *J. A. M. A.* **93**:692 (Aug. 31) 1929. (g) Key, J. A.: Pathogenic Properties of Organisms Obtained from Joints in Chronic Arthritis, *Proc. Soc. Exper. Biol. & Med.* **26**:863 (June) 1929. (h) Shands, A. R.: Synovial Fluid in Infectious and Neuropathic Arthritis, *South. M. J.* **23**:818 (Sept.) 1930. (i) Margolis, H. M., and Dorsey, A. H. E.: Bacteriology of the Blood in Chronic Infectious Arthritis, *J. Infect. Dis.* **46**:442 (June) 1930; Chronic Arthritis: Bacteriology of Affected Tissues, *Arch. Int. Med.* **46**:121 (July) 1930. (j) Nye, R. N., and Waxelbaum, E. A.: Streptococci in Infectious (Atrophic) Arthritis and Rheumatic Fever, *J. Exper. Med.* **52**:885 (Dec.) 1930. (k) Klugh, G. F.: Streptococci from Blood Cultures in Arthritis, *South. M. J.* **24**:706 (Aug.) 1931. (l) Bernhardt, H., and Hench, P. S.: Bacteriology of the Blood in Chronic Infectious Arthritis, *J. Infect. Dis.* **49**:489 (Dec.) 1931. (m) Dawson, M. H.; Olmstead, M., and Boots, R. H.: Bacteriologic Investigations on the Blood, Synovial Fluid, and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, *Arch. Int. Med.* **49**:173 (Feb.) 1932. (n) Cadham, F. T.: A Discussion on the Etiology and Specific Treatment of Arthritis, *Canad. M. A. J.* **26**:287 (March) 1932. (o) Strauss, A.: Problems in the Relation of Streptococci and Diphtheroid Bacilli to Chronic Infectious Arthritis, *Virginia M. Monthly* **58**:801 (March) 1932. (p) Clawson, B. J., and Wetherby, M.: An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients, *Ann. Int. Med.* **5**:1447 (June) 1932. (q) Lichtman, S. S., and Gross, L.: Streptococci in the Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases, *Arch. Int. Med.* **49**:1078 (June) 1932. (r) Coste, F., and Forestier, J.: Streptocoque et rhumatisme chronique, *Presse méd.* **40**:1589 (Oct. 22) 1932. (s) Ashworth, O. O.: Bacteriology and Treatment of Rheumatoid Arthritis, *Virginia M. Monthly* **59**:452 (Nov.) 1932.

present report summarizes the results of 232 such cultures of synovial fluid and tissue made during the past three years.

Rheumatoid arthritis is represented in this series by 55 cultures, and Still's disease by 2; thus 57 cultures were made of synovial fluid and tissue of patients suffering from so-called chronic multiple infectious arthritis. The remaining 175 cultures may be considered as controls for the cases of arthritis; the great majority were derived from more or less chronic conditions of the joints, both infectious and noninfectious, such as chronic osteo-arthritis, effusions into the knee joint secondary to direct injuries or to tears of the semilunar cartilage, tuberculosis of the joint, gonorrheal infection of the joint, conditions diagnosed as syphilitic involvement of the joints and other miscellaneous conditions of the joints with effusions that were definitely not the result of rheumatoid arthritis.

In classifying the various conditions of the joints, the clinical histories were studied carefully, and all available diagnostic criteria were considered. The patients in the group with rheumatoid arthritis presented the typical syndrome of a chronic polyarthritis, which tended to progress to ankylosis and deformity. Many patients presented the fusiform fingers often found in this disease. The ages of the majority of the persons of this group varied between 10 and 40 years. All degrees of severity of the disease are included in the series. The patients in the group with osteo-arthritis were older (all but three of the forty-two patients being over 40 years of age); hypertrophic changes were demonstrable roentgenographically; no complete ankylosis of the joint (usually the knee) was present; motion was frequently painful, and crepitation could often be detected. All of the tuberculous joints were proved to be of a tuberculous nature by inoculation of guinea-pigs, by culture of synovial fluid or tissue,⁴ or by histologic examination of material removed from a joint at operation. The clinical diagnosis of gonorrheal infection of a joint was confirmed by gonococcus fixation tests on the synovial fluid and, in some cases, by isolation of the specific organism. Confirmation of the clinical diagnoses of the various other conditions of the joints was derived from roentgenographic, operative or pathologic examination.

TECHNIC

At the beginning of the work a variety of culture mediums was used. These included beef heart infusion containing dextrose, or dextrose plus ascitic fluid, and infusion of human placenta to which was added dextrose or dextrose and calcium carbonate. In addition, Bacto-brain-heart infusion was employed, as it had given good results in routine cultures. The various special mediums appeared to have

4. Blair, J. E., and Hallman, F. A.: Diagnosis of Surgical Tuberculosis: Comparison of Diagnosis by Inoculation of Guinea-Pigs and by Culture, *Arch. Surg.* **27**:178 (July) 1933.

no particular advantage over the Bacto-brain-heart infusion, and the latter medium was finally used exclusively. It was prepared according to the prescribed directions, and sterilized in the autoclave at from 15 to 18 pounds' (6.8 to 8.1 Kg.) pressure for twenty minutes. The final p_H was from 7.2 to 7.4. For a solid medium, 2 per cent of flaked agar was added. For subcultures, this infusion medium was used alone, or with the addition of human or rabbit blood.

When possible, specimens were cultured soon after they were obtained, although some of the specimens were not received from the clinic until the next day. Aerobic and anaerobic cultures of broth and agar were made of each specimen; for the anaerobic cultures Buchner tubes were employed.

The cultures were examined daily for visible growth for the first week, then at intervals of about a week for a total period of six weeks. At the end of this time, gram-stained smears from each tube were examined before the tubes were discarded. When cultures were found to be positive, they were immediately subcultured. The subcultures were examined daily for growth, and second subcultures were made from these after five days, whether or not visible growth was present.

RESULTS

Rheumatoid Arthritis.—In this group, 55 cultures were made of material from forty-four patients. Forty-seven synovial fluids, five lymph glands, two synovial membranes and one subcutaneous nodule were cultured. All but two of the synovial fluids were obtained from knee joints; one was aspirated from a wrist joint and one from an ankle joint. Of the 55 cultures, 41 (74.5 per cent) remained sterile throughout the entire period of observation; these included cultures of thirty-seven synovial fluids, two lymph glands, one subcutaneous nodule and one synovial membrane.

In 14 cultures (25.4 per cent) micro-organisms were obtained after periods of incubation varying from one to four weeks. These 14 cultures represented ten synovial fluids, three lymph glands and one synovial membrane. The specimens yielding positive cultures were obtained from a group of persons in whom the duration of arthritic symptoms ranged from a few months to fifteen years.

The organisms obtained in these cultures were: streptococci, three (including two indifferent strains and one unidentified streptococcus); diphtheroid bacilli, two; gram-positive cocci occurring in pairs or short chains, six; gram-positive coccoid bacillus and a gram-negative bacillus, two; a gram-positive coccus and a large gram-negative bacillus, one. The streptococci and diphtheroid bacilli usually were cultured without much difficulty. However, in the other cultures, while the cocci mentioned were found in smears of the sediment after prolonged incubation, it was usually impossible to obtain satisfactory growth even after repeated attempts to subculture.

Still's Disease.—One synovial fluid from a patient with Still's disease remained sterile. One lymph gland from another patient with the same disease gave a growth of gram-positive diplococci which were never successfully subcultured.

Organisms Occurring in Cultures from Synovial Fluid and from Tissues

Chronic Multiple Arthritis	Total Number Cultures	Sterile	Positive	Organisms Isolated	Comment
Rheumatoid arthritis.....	55	41 (74.5%)	14 (25.4%)	<div> <div> 3 Streptococci { 2 inert 1 unidentified 2 Diptheroid bacilli 6 Gram-positive cocci 2 Gram-positive cocci and gram-negative bacillus </div> <div> 1 Gram-positive coccus and large gram-negative bacillus 1 Gram-positive diplococcus </div> </div>	<div> From synovial fluid and synovial tissue of same patient From synovial fluid From synovial fluids From synovial fluids (3); from lymph glands (3) From synovial fluids, both from same patient at interval of 1 month (synovial tissue, 1 month after second aspiration, sterile) From synovial fluid (3 other fluids from same patient sterile) From axillary gland. The sterile culture was from synovial fluid </div>
Still's disease.....	2	1	1		
Total.....	57	42 (73.6%)	15 (26.3%)		
Controls					
Osteo-arthritis.....	42	35 (83.3%)	7 (16.6%)	<div> <div>2 Streptococci, unidentified 2 Diptheroid bacilli 1 Staph. aureus 2 Gram-positive cocci</div> <div>3 Streptococci, inert 2 Diptheroid bacilli 1 Staph. aureus 1 Gram-positive coccus</div> </div>	All from synovial fluid
Synovitis.....	45	38	7		
Miscellaneous effusions of joints	17	17	0		
Tuberculous joints.....	14	10	4	<div>2 Mycobacterium tuberculosis* 1 Staph. aureus and diptheroid 1 Gram-positive coccus</div>	
Gonorrheal infection of joints	15	10	5	5 Diplococcus gonorrhoeae	
Joints with syphilitic involvement	14	11	3	<div>1 Diptheroid bacillus 1 Gram-positive coccus 1 Small gram-negative bacillus</div>	
Miscellaneous fluids and tissues	28	21	7	<div>3 Staph. aureus 2 Streptococci { 1 inert 1 unidentified 1 Gram-positive diplococcus 1 Mixed culture: Staph. aureus; coli; gram-positive diplococcus</div>	<div>From fluids of bursae From inguinal gland, adenitis From cervical gland, tuberculous adenitis From hematoma of knee From cyst of popliteal space</div>
Total.....	175	142 (81.1%)	33 (18.8%)		

* It should be emphasized that these cultures were obtained on routine culture mediums, in contrast to the special mediums usually employed for the isolation of tubercle bacilli.

Controls.—Excluding the cultures from the group with rheumatoid arthritis and with Still's disease, and considering the remaining 175 cultures as a group of controls, we found that 142 (81.1 per cent) were sterile and 33 (18.8 per cent) were positive. As indicated, these cultures were made of material from patients with a variety of more or less chronic infectious and noninfectious conditions of the joints.

The micro-organisms occurring in these cultures are varied in kind (table). They include *Staphylococcus aureus*, streptococci, gram-positive cocci incapable of growth on subculture, diphtheroid bacilli and occasional gram-negative bacilli. Thus there is no particular difference, in this series, between the micro-organisms isolated from either synovial fluids or tissues of patients with rheumatoid arthritis or from specimens obtained in a group with wholly unrelated conditions of the joints. No organism which could be interpreted as possessing etiologic significance was obtained consistently in the group with rheumatoid arthritis. The organisms isolated in this group all have their counterparts in the control group. In addition, among the positive cultures of the control group were found a few staphylococci and also gonococci and tubercle bacilli.

It is of interest to record that in the fifteen cases of gonorrheal arthritis, the 5 positive cultures were all pure cultures of *Diplococcus gonorrhoeae*; all of these cultures grew readily on the routine medium which we employed. Two pure cultures of tubercle bacilli were obtained in the series of fluids from tuberculous joints cultured on the routine medium. These cultures were visible as small colonies at the bottom of the tubes of broth after six weeks of incubation. In a previous report⁴ we have recorded the isolation of tubercle bacilli in a large percentage of cultures from fluids and tissues of tuberculous joints, using special culture mediums. However, the occurrence of cultures of tubercle bacilli on the routine medium appears to be worthy of mention.

COMMENT

A question arises as to the significance of the organisms which have been isolated by various investigators in cultures of synovial fluids and tissues from cases of rheumatoid arthritis and in cultures from cases which served as controls. As stated, the positive cultures which have been obtained represent a variety of bacteria, including streptococci, staphylococci, diphtheroid bacilli and occasionally other organisms. All of these bacteria have been isolated, not only in cases of rheumatoid arthritis, but frequently also in the wholly unrelated conditions of the joints which served as controls. Furthermore, the reports of various groups of laboratory workers have been conflicting as to both the kind and the number of micro-organisms obtained. Considered from the point of view of etiology, a brief survey of recent papers dealing with

the bacteriology of rheumatoid arthritis is sufficient to demonstrate that at present a convincing consistency of results has not been obtained.

Reviews of the bacteriologic work done during the past few years in regard to the etiology of rheumatoid arthritis may be found in several of the recent contributions, e.g., that of Jordan.⁵ A critical review of the results which have been obtained is not within the province of this report. However, it may be mentioned that several conditions of the joints are included in some of the reports, without distinction as to clinical diagnosis, thus detracting from any significance which might otherwise be attached to the results. The culture mediums and the technic employed vary considerably, and in some cases the methods used are not described. These and other factors render an evaluation of the results extremely difficult. It is evident, however, that a multiplicity of micro-organisms has been obtained from synovial fluids and tissues in both rheumatoid arthritis and entirely unrelated conditions of the joints.

From a study of the varied bacteriologic results recorded, it is obvious that any one of several interpretations may reasonably be given. It is possible that all of the organisms isolated may be capable of inciting changes in the joint characteristic of rheumatoid arthritis, or none may be of etiologic significance, all being present fortuitously as invaders of the diseased joint. The suggestion has been offered that certain of the streptococci isolated may be laboratory contaminations.^{3j, m} Dawson, Olmstead and Boots^{3m} reported the isolation on two occasions of *Streptococcus viridans* from sterile agar subjected to the several manipulations involved in the technic of the Cecil blood culture. Cecil maintains that he has never recovered a streptococcus on repeated exposure of plates to the air of the laboratory.² We also have exposed plates to the air of the laboratory, and to that of the operating room during operations, and we have not encountered colonies of streptococci on such plates.

Having obtained streptococci in over 60 per cent of cultures from the blood and joints in cases of rheumatoid arthritis, Cecil, Nicholls and Stainsby "have set forth the proposition that rheumatoid arthritis is a streptococcal infection." Crowe,^{3c} on the other hand, expressed the belief that the etiologic agent of rheumatoid arthritis is a staphylococcus, to which he has given the name *Micrococcus deformans*. It is obvious that these or any other results must have more or less general confirmation to be convincing.

It is true that streptococci have frequently been isolated from the blood or joints of persons with rheumatoid arthritis, but it should be pointed out that the same organisms have not infrequently been obtained

5. Jordan, E. P.: The Microbic Etiology of Rheumatic Fever and Arthritis. Arch. Path. 10:79 (July) 1930.

in control cultures. Furthermore, in some laboratories all varieties of streptococci, as well as other micro-organisms, have been isolated, but no consistency of results has occurred, even under supposedly uniform working conditions. The lack of corroborative results of any one report becomes more manifest with each addition to the already long list of bacteriologic reports. The one exception has been cited.

Jordan⁵ suggested that there are two explanations compatible with the repeated isolation of various streptococci: "that arthritis can be caused by streptococci of many types, not specific, or that the streptococcus of arthritis has many inconstant features. The doctrine of microbic dissociation, as developed by Hadley and others may serve as the ultimate explanation for such apparent inconsistency." It would appear that dissociation deserves careful consideration from this point of view. The literature contains numerous isolated observations of variations of streptococci from the normal, all of which, when considered together, indicate that the phenomenon of dissociation may have been in operation. We have repeatedly observed varying degrees of pleomorphism in cultures of streptococci, and forms closely resembling cocci in cultures of diphtheroid bacilli; these observations are undoubtedly not uncommon in other laboratories. A relationship between diphtheroid bacilli and streptococci has been demonstrated by Mellon⁶ and by Ramsin and Givkovitch.⁷ The transformation of one to the other form has been reported by Koch and Mellon,⁸ Straus³⁰ and Cooley.⁹ In view of these observations it would seem that the frequent isolation of diphtheroid bacilli from cases of chronic arthritis should receive consideration. It is by no means to be assumed that every diphtheroid bacillus so isolated represents a dissociated streptococcus. However, a careful study of the possibility of these relationships in rheumatoid arthritis seems to be desirable. Information thus obtained would be of service in evaluating the claims which have been made regarding the rôle of streptococci in this disease. Even if diphtheroid bacilli obtained from cases of rheumatoid arthritis should be shown to be closely related to the streptococci from these sources, the problem still remains of explaining the inconstancy of their isolation and their occurrence in some control cultures.

6. Mellon, R. R.: Studies in Microbic Heredity: V. The Biogenetic Law of Haeckel and the Origin of Heterogeneity Within Pure Lines of Bacteria, *J. Bact.* **11**:203 (March) 1926.

7. Ramsin, K., and Givkovitch, M.: Transformations du streptocoque hémolytique, *Compt. rend. Soc. de biol.* **95**:952 (Oct. 29) 1926.

8. Koch, R., and Mellon, R. R.: The Biological and Clinical Significance of Diphtheroids in the Blood Stream, *J. Bact.* **19**:25 (Jan.) 1930.

9. Cooley, L. E.: Dissociation of Streptococci, *J. Infect. Dis.* **50**:358 (April) 1932.

In the development of the hypothesis that streptococci play an etiologic rôle in rheumatoid arthritis, considerable emphasis has been placed on the frequent occurrence in this disease of the so-called foci of infection, from which streptococci may often be isolated. While cultures of various foci yield streptococci in a large number of cases, it should be remembered that other bacteria may also be isolated from these foci, notably staphylococci and diphtheroid bacilli. The latter organisms cannot be ignored if foci are assumed to be the source of infection in rheumatoid arthritis. Furthermore, many adults who show no indications of rheumatoid arthritis harbor these same organisms in similar foci. Certain constitutional and environmental factors, of course, may play a contributory rôle in the development of the disease.

If rheumatoid arthritis is of infectious nature, it would seem that a disproportionately large number of synovial fluids yield sterile cultures. Since the course of the disease is protracted, it has been assumed that the organisms originally inciting the disease processes are gradually destroyed or removed by the defense mechanisms of the body. As pointed out by Margolis and Dorsey, in their series the average duration of the symptoms was a matter of months or years, and absolute quiescence of the process was a prerequisite for the reconstructive operations which supplied material for their cultures. They assumed that the few positive cultures obtained represented organisms which "retained their viability despite the natural reparative processes which had been exerted by the affected tissues over periods of months or years."³¹ On the other hand, the conviction has been voiced by other investigators that it would be difficult to conceive of streptococci which possessed sufficient vitality to remain in or about affected joints for such long periods.³¹

Until evidence to the contrary is offered it appears reasonable to assume that rheumatoid arthritis is caused by no one specific etiologic agent, either infectious or noninfectious. It must be assumed that in many cases numerous factors are at work. Undoubtedly there are cases of rheumatoid arthritis in which the onset was the result of infection, although the specific organism cannot be identified. The hypothesis of the relation of allergy to rheumatic fever, which has been developed by Swift and his co-workers,¹⁰ Zinsser¹¹ and others, may reasonably be applied also to rheumatoid arthritis. Experimental attack on the relation of allergy to arthritis has been made by Freiberg¹² and deserves to be carried further.

10. Swift, H. F.: Rheumatic Fever, *J. A. M. A.* **92**:2071 (June 22) 1929.

11. Zinsser, H., and Yu, H.: The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, *Arch. Int. Med.* **42**:301 (Aug.) 1928.

12. Freiberg, J. A.: Allergy as a Factor in the Production of Proliferative Arthritis, *Arch. Surg.* **18**:645 (Feb.) 1929.

SUMMARY AND CONCLUSIONS

1. In a series of 57 cultures of synovial fluids and tissues from chronic multiple arthritis (55 from rheumatoid arthritis and 2 from Still's disease), a total of 41 (74.5 per cent) remained sterile and 14 (25.4 per cent) yielded positive cultures. The micro-organisms obtained in the positive cultures included streptococci, diphtheroid bacilli, gram-positive cocci incapable of growth on subculture and an occasional gram-negative bacillus associated with the aforementioned bacteria.

2. In a series of 175 cultures of synovial fluids and tissues from a variety of chronic infectious and noninfectious conditions of the joint other than rheumatoid arthritis, 142 (81.1 per cent) were sterile and 33 (18.8 per cent) were positive. The positive cultures included *Staphylococcus aureus*, indifferent streptococci, gram-positive cocci incapable of growth on subculture and diphtheroid bacilli.

3. No direct etiologic significance is attached to any of the organisms obtained in this series.

4. It is felt that at the present time no specific bacteriologic agent may be considered to have been demonstrated as the etiologic cause of rheumatoid arthritis, particularly in view of the multiplicity of results and the lack of general confirmation of any one report.

CLINICAL CONSIDERATION OF THE ETIOLOGY OF PEPTIC ULCER

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Benign duodenal, gastric and anastomotic ulcers are usually referred to as peptic ulcers because they are invariably to be found in regions subjected to the bathing influence of the acid chyme and because it is assumed that the eroding action of the gastric juice is of paramount significance in their development. There are still many factors regarding the etiology, course and chronicity of the lesions which remain imperfectly understood. Even a cursory review of the literature on the subject is convincing evidence of the complexity of the problem. It is my purpose here to review briefly a few of the more important hypotheses advanced to explain the genesis and the course of peptic ulcer. I shall attempt also to arrange the various hypotheses so as to make them apply in a practical manner to the problem of ulcer in man.

HYPOTHESES CONCERNING THE CAUSE OF PEPTIC ULCER

Circulatory Disturbances.—Virchow¹ was under the impression that disturbance of the veins and the arterioles of the submucosa finally resulted in localized necrosis of the muscularis and the mucous membrane. The peptic action of the acid gastric chyme would then cause the ulceration. Hauser² and, more recently, Eggers³ suggested that hemorrhagic infarcts are the immediate pathologic processes that eventually result in necrosis of the gastro-intestinal mucosa. W. J. Mayo⁴ described an anemic spot on the anterior surface of the duodenum. He expressed the belief that this area might be increasingly vulnerable to the development of ulceration because of circulatory

From the Division of Medicine, the Mayo Clinic.

1. Virchow, Rudolph: Historisches, kritisches und positives zur Lehre der Unterleibsaffektionen, Virchows Arch. f. path. Anat. 5:281, 1853.

2. Hauser, G.: Die peptischen Schädigungen des Magens, des Duodenums und der Speiseröhre und das peptische postoperative Jejunalgeschwür, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, part 1, p. 339.

3. Eggers, H.: Gastritis und konstitutionelle Innervations- und Zirkulationsstörungen, Deutsche med. Wchnschr. 55:957 (June 7) 1929.

4. Mayo, W. J.: Pathologic Data Obtained from Ulcers Excised from the Anterior Wall of the Duodenum, Ann. Surg. 57:691 (May) 1913.

deficiency. Reeves⁵ noted poor vascularization of the first portion of the duodenum and the pyloric portion of the lesser curvature, and suggested that in consequence of this there was localized ischemia with increasing vulnerability of the tissues to vascular insults. Wilkie⁶ mentioned that the factor of chronicity might well be related to the impoverished vascularization of the pylorus and the first portion of the duodenum. Reeves noted attenuation of the speed of the blood current as it traverses the small arteries of the mucosa, thus, he felt, rendering the areas particularly liable to local embolism and thrombosis. Payr⁷ tied off large vessels to the stomach; occasionally this resulted in acute ulceration in the areas supplied by the vessels. He found that the introduction of a dilute solution of formaldehyde into a small gastric artery would often result in chronic and even in perforating gastric ulcers. He found that the lumen of the infected vessels had been greatly narrowed by this procedure, the blood supply to localized areas within the wall of the stomach thus being decreased. Gallagher⁸ was able to produce acute ulcers in the duodenum by rendering the localized areas anemic for thirty minutes by means of clamping the mucosa.

Erosion of Tissue by Acid.—Sippy,⁹ Bolton,¹⁰ Hurst and Stewart,¹¹ Morton¹² and, more recently, Mann,¹³ Dragstedt,¹⁴ Matthews¹⁵ and

5. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, *Surg., Gynec. & Obst.* **30**:374 (April) 1920.

6. Wilkie, D. P. D.: The Blood Supply of the Duodenum with Special Reference to the Supraduodenal Artery, *Surg., Gynec. & Obst.* **13**:399 (Oct.) 1911.

7. Payr, Erwin: Experimente über Magenveränderungen als Folge von Thrombose und Embolie im Pfortadergebiete, *Arch. f. klin. Chir.* **84**:799, 1907.

8. Gallagher, W. J.: Acute Traumatic Ulcers of the Small Intestine; Observations on the Effects of Application of Clamps on the Gastro-Intestinal Tract: An Experimental Study, *Arch. Surg.* **15**:689 (Nov.) 1927.

9. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice Corrosion, *J. A. M. A.* **64**:1625 (May 15) 1915.

10. Bolton, Charles: Ulcer of the Stomach, London, Edward Arnold & Co., 1913.

11. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

12. Morton, C. B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer; a Consideration of Etiology, *Ann. Surg.* **85**:207 (Feb.) 1927.

13. Mann, F. C.: The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, *S. Clin. North America* **5**:753 (June) 1925.

14. Dragstedt, L. R.: Contributions to the Physiology of the Stomach: XXXVIII. Gastric Juice in Duodenal and Gastric Ulcers, *J. A. M. A.* **68**:330 (Feb. 3) 1917.

15. Matthews, W. B.: Production of Intestinal Ulcers by Active Gastric Juice, *Proc. Soc. Exper. Biol. & Med.* **28**:960, 1931.

many others pointed out the part played by the eroding action of abnormally acid gastric juice in the production and the persistence of peptic ulceration. Hurst and Stewart noted that the lesions were confined to the portions of the stomach and the duodenum that are habitually bathed with acid chyme. Moszkowicz¹⁶ assumed that hyperacidity of the gastric secretion injures the wall of the stomach in the region of the fundic glands, particularly in the region of the lesser curvature, and that the wall of the intestine is likewise susceptible to similar trauma, whereas within the stomach the portion including the pyloric glands seems to be partly protected. With Silbermann¹⁷ and Büchner,¹⁸ Moszkowicz assumed that psychically stimulated gastric juice is the cause of erosions of the mucosa.

Neurogenic Factor.—Von Bergmann¹⁹ and many other observers considered that derangement of the nervous system was the most significant single factor in the causation of peptic ulceration. Some derangement of the function of the sympathetic and parasympathetic nervous system is considered by advocates of this hypothesis to result eventually in localized spasmophilia of the duodenal or gastric musculature, with consequent areas of mucosal or submucosal ischemia. In consequence, there is a diminished resistance in the localized areas which results eventually in erosion of the mucosa. The prolonged continuation of this nervous irritability tends to the production of chronic ulcer. Singer,²⁰ more specifically, defined hyperirritability or actual neuritis of the vagus nerve as the cause of peptic ulcer. Hartzell²¹ showed that section of the vagus nerve definitely decreases, at least for a time, the acidity of gastric secretion.

It might thus be postulated that the increase in the activity of the vagus nerve brought about by increasing the rate of secretion of the gastric acids tends to increase the incidence of ulcer. Beaver and Mann²² showed that dissection of the vagus nerves of the stomach prevents the occurrence of ulcers in some instances following certain opera-

16. Moszkowicz, Ludwig: Ueber die Entstehung der Magengeschwürkrankheit (Gastropathie), *Klin. Wchnschr.* **9**:385 (March 1) 1930.

17. Silbermann, I. S.: Experimentelle Magen-Duodenalulcuserzeugung durch Scheinfüttern nach Pawlow, *Zentralbl. f. Chir.* **54**:2385 (Sept. 11) 1927.

18. Büchner, Franz: Magensaft, Gastritis und peptisches Geschwür, *Klin. Wchnschr.* **9**:1, 1930.

19. von Bergmann, G.: *Ulcus duodeni und vegetatives Nervensystem*, Berl. klin. Wchnschr. **50**:2374, 1913.

20. Singer, Gustav: Peptisches Geschwür—Lungentuberkulose—anatomische Vaguserkrankung, *Arch. f. Verdauungskr.* **43**:410 (March) 1928.

21. Hartzell, J. B.: The Effect of Section of the Vagus Nerves on Gastric Acidity, *Am. J. Physiol.* **91**:161 (Dec.) 1929.

22. Beaver, M. D., and Mann, F. C.: The Production of Peptic Ulcer After Section of Gastric Nerve, *Ann. Surg.* **94**:1116 (Dec.) 1931.

tions which would otherwise tend to produce ulcers. Cushing²³ was of the opinion that irritative disturbance of either fiber tracts or vagal centers in the brain stem is responsible for ulcer in certain instances.

Inflammation and Infection.—Konjetzny,²⁴ Orator and Metzler²⁵ and Puhl,²⁶ among others, have stated their belief that duodenal and gastric ulcers are the results of inflammatory processes, with destruction of tissues, which begin at the surface of the mucous membrane and from there gradually spread into the depths of the tissues. They are of the opinion that the lesions never develop in healthy mucosa, but always as a result of gastritis or duodenitis. Lebert²⁷ and Cohn²⁸ injected pus intravenously into experimental animals and produced acute lesions in the stomach and duodenum, thus adding to the evidence that infection is a cause of ulcer. Letulle²⁹ injected streptococci and staphylococci intravenously into animals and was able to produce acute ulcer of the stomach. Bezançon and Griffon³⁰ produced acute gastric ulcers after the experimental intravenous injection of pneumococci. Turck³¹ produced round ulcers of the stomach and duodenum in dogs after feeding them colon bacilli over a prolonged period. In 1913, by intravenous injection of streptococci of the proper grade of virulence, Rosenow³² produced ulcer of the stomach and the duodenum in animals; he believed that the ulcers were due to a localized infection and a secondary digestion of the gastric mucosa. He later advanced the hypothesis that the usual form of gastroduodenal ulcer may be due to

23. Cushing, H.: Peptic Ulcers and the Interbrain, Surg., Gynec. & Obst. **55**:1 (July) 1932.

24. Konjetzny, G. E.: Die chronische Gastritis des Ulcusmagens (zur Beurteilung der Operationsanzeigen und der Operationserfolge beim Magen-Duodenalgeschwür), Zentralbl. f. Chir. **50**:1026 (June 30) 1923.

25. Orator, V., and Metzler, F.: Klinische und experimentelle Beiträge zur Ulcusfrage: III. Zur Frage der Pathogenese und malignen Entartung des Magen-Duodenalgeschwürs, Deutsche Ztschr. f. Chir. **202**:167 (May) 1927.

26. Puhl, E.: Ueber die Entstehung und Entwicklung des Magen-Duodenalgeschwürs, Arch. f. klin. Chir. **158**:1, 1930.

27. Lebert, quoted by Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333 (Sept.) 1916.

28. Cohn, B.: Klinik der embolischen Gefäßerkrankheiten mit besonderer Rücksicht auf die ärztliche Praxis, Berlin, A. Hirschwald, 1860, vol. 16, p. 696.

29. Letulle, Maurice: Origine infectieuse de certains ulcères simples de l'estomac ou de duodénum, Bull. et mém. Soc. méd. d. hôp. de Paris **5**:360 (Aug. 10) 1888.

30. Bezançon, F., and Griffon, F.: Ulcérations gastriques au cours de la septicémie pneumococcique chez le cobaye, Bull. et mém. Soc. anat. de Paris **74**:409 (May) 1899.

31. Turck, F. B.: Further Observations on the Etiology and Pathology of Peptic Ulcer, Brit. M. J. **1**:922 (April 20) 1907.

32. Rosenow, E. C.: The Production of Ulcer of the Stomach by the Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913.

localized infection by streptococci having a special elective affinity for the mucous membrane of the stomach and the duodenum. In 1924, he³³ reported the isolation, from excised ulcers and from foci of infection in patients suffering from peptic ulcer, of streptococci which had a selective affinity for the stomach and duodenum when they were injected intravenously into animals and which in many instances produced hemorrhage and ulceration. Further evidence corroborating the impressions of Rosenow was adduced by Meisser,³⁴ who produced chronic foci of infection in dogs by devitalizing some of their teeth and making injections into them of streptococci obtained from the infected teeth of patients suffering from ulcer of the stomach. Hemorrhage or ulceration of the gastroduodenal mucosa was produced in many of these dogs.

Evidence to support the foregoing hypotheses is supplied by the multiplicity of ways in which ulcers have been produced experimentally. In most instances, the experiments resulted in the production of acute ulcers or mucosal erosions which had a tendency to heal rapidly and which, as a rule, did not have the general characteristics of ulcers in man. Mann and Williamson³⁵ described a method for producing in animals a chronic ulcer which was similar in most respects histologically to peptic ulcer in man. They drained the duodenal secretions, as well as the bile and pancreatic juice, into the terminal part of the ileum and then transplanted loops of jejunum or ileum into the position usually occupied by the duodenum. Following this procedure, subacute ulcer usually developed beyond the pylorus in the jejunal mucosa just distal to the line of suture. Mann and Williamson believed that the chemical action of the acid chyme, which was undiluted by duodenal content, on the jejunal mucous membrane was the cause of the ulceration, and that the mechanical factor of impingement of the acid chyme on the jejunum, through the pylorus, had an effect in producing the lesions and in particular, perhaps, in determining the site of the ulcers.

Matthews and Dragstedt³⁶ added corroboration of the factor of acid erosion as a cause in the production of ulcer. They adduced evidence by various operative procedures on animals to suggest that the chemical action of pepsin-hydrochloric acid, particularly in concentration

33. Rosenow, E. C.: *Experimental and Clinical Studies on Focal Infection and Elective Localization; Newer Findings and Their Significance*, J. Am. Dent. A. **11**:963 (Oct.) 1924; Dental Sum. **44**:954 (Nov.); 1026 (Dec.) 1924.

34. Meisser, J. G.: *Further Studies on Elective Localization of Bacteria from Infected Teeth*, J. Am. Dent. A. **12**:554 (May) 1925.

35. Mann, F. C., and Williamson, C. S.: *The Experimental Production of Peptic Ulcer*, Ann. Surg. **77**:409 (April) 1923.

36. Matthews, W. B., and Dragstedt, L. R.: *The Etiology of Gastric and Duodenal Ulcer*, Surg., Gynec. & Obst. **55**:265 (Sept.) 1932.

in pure, undiluted gastric juice, can by itself produce typical chronic progressive ulcers in the stomach, duodenum, jejunum, ileum or colon. They reproduced experimentally a counterpart of the ulcer of Meckel's diverticulum in man by implanting a small isolated pouch of gastric wall into the jejunum and ileum. This resulted in progressive ulcers in the jejunum in 85 per cent of the experiments, and when the isolated pouch was implanted into the ileum, in 100 per cent. The result was cited as a remarkable example of the susceptibility of an organism's living tissue to the irritating action of pure, undiluted gastric juice. Mann and Bollman³⁷ also demonstrated a definite gradient in susceptibility to ulcer of the duodenum, jejunum and ileum, suggesting that the ileum is much more sensitive to the formation of ulcer than the part of the bowel ordinarily accustomed to receiving the acid chyme.

A similar gradient in susceptibility was suggested by Harper,³⁸ who attached a piece of ileum to an isolated gastric pouch and produced ulcer in practically all experiments. He performed the same operation by using strips of duodenum, and found that the upper part of the small bowel was much more resistant to the acid-eroding action of the gastric pouches, and that ulcers occurred much less frequently. Experimental work thus gives conclusive evidence that the eroding action of undiluted gastric juice is undoubtedly one of the chief factors in the production of chronic ulcer. No hypothesis for the formation of peptic ulcer in man can possibly omit the consideration of these pertinent observations. It is extremely doubtful, however, that it will become possible to place the sole responsibility for the genesis of ulcer and its subsequent behavior through the life cycle on this single cause.

ULCER DIATHESIS

Many investigators have observed that certain persons are particularly liable to the development of peptic ulcer; this has led to the postulation that there must be some definite anatomic or physiologic abnormality which increases the susceptibility of these persons to the development of ulcer. Draper³⁹ stated that certain anthropometric relations as well as certain psychologic factors are characteristic of the ulcer-bearing patient, and he referred to these measurable components as "the ulcer constitution." Similar observations were made

37. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcer; Development and Treatment, *J. A. M. A.* **99**:1576 (Nov. 5) 1932.

38. Harper, F. R.: Development of Experimental Peptic Ulcer; Changes in Acidity and Treatment, *Proc. Staff Meet. Mayo Clin.* **7**:318 (June 1) 1932.

39. Draper, George; Dunn, H. L., and Seegal, David: Studies in Human Constitution: I. Clinical Anthropometry, *J. A. M. A.* **82**:431 (Feb. 9) 1924.

by Stenbuck,⁴⁰ who expressed the belief that there is something characteristic in the appearance of the patients. Their faces are usually thin and drawn, with high malar prominences; they are poorly nourished and energetic in demeanor, and present an anxious expression. Other observers believe that a "vasoneurotic diathesis" is the required condition preceding the development of peptic ulcer.

Müller and Heimberger⁴¹ examined fresh specimens with a capillary microscope immediately following partial gastrectomy. They found spasm and atony of the arterioles, capillaries and venules of the gastric mucous membrane. They intimated that they could also demonstrate similar vascular abnormalities in the mucous membrane of the lips and in the skin of their patient. They assumed that this diathesis was the result of congenital or acquired disharmony in the structure and the function of the peripheral blood vessels.

Hurst and Stewart described hypersthenic gastric diathesis and intimated that it is an inborn variation from the average normal which manifests itself in a short stomach accompanied by active peristalsis and rapid evacuation, and in hyperchlorhydria with gastric hypersecretion. Although they admitted that the condition is compatible with the perfect function of the digestive organs, they expressed the belief that it is one of the essential predisposing factors in the production of duodenal ulcer. They stated that persons with long stomachs, if exposed to the exciting causes of ulceration, are likely to have gastric rather than duodenal ulcers.

VARIOUS HYPOTHESES IN THE PROBLEM OF ULCER IN MAN

In reviewing the various hypotheses advanced by physiologists to explain the genesis of ulcer, it must be mentioned that the hypotheses usually represent successful efforts in the production of ulcer in experimental animals. No doubt much valuable information is thus acquired, but it is difficult to condense and correlate it into the problem of ulcer in man. Confusion soon results when an attempt is made to apply a specific single cause for ulcer to the heterogenous clinical complexities of the behavior of the syndrome initiated by ulcer in man.

In all probability, the picture puzzle of ulcer will be satisfactorily conjoined only by the application and the correlation of the combined knowledge accumulated by physiologists, pathologists, surgeons and clinicians. When the information obtained by physiologists withstands the critical analysis of clinicians and is practical in its application to the

40. Stenbuck, J. B.: A Description of the Type of Facies Found in Cases of Ulcer of the Stomach and Duodenum, *Am. J. Surg.* **38**:181 (Aug.) 1924.

41. Müller, Otfried, and Heimberger, Hermann: Ueber die Entstehung des runden Magengeschwürs, *Deutsche Ztschr. f. Chir.* **187**:33 (Aug.) 1924.

diverse problems of ulcer in man, and when clinical facts can be taken by the physiologist and correlated with experience in the laboratory, the disjointed segments of the puzzle of peptic ulcer will have been approximated to the ultimate solution of this most important problem.

A careful analysis of the causes assigned for the formation of ulcer reveals that many are not at all applicable to the problem of ulcer in man, and that others apply only in a limited degree. I have attempted to rearrange certain of the important hypotheses concerning the formation of ulcer into a clinical classification which seems applicable to the problem in man. Peptic ulcer is probably the result not of a single factor but of several interacting factors; these will be considered separately. The factors can best be summarized under three heads: (1) the factor of trauma to tissue, (2) the factor of aggression and defense and (3) systemic factors.

Factor of Trauma to Tissue.—Under this heading can be considered all the traumatizing influences which cause or accompany the original aberration from its normal state in the mucous membrane or in the wall of the viscus. There may be involvement from the mucosa downward. There may be disturbances in the submucosal tissue, which by virtue of its consequent loss of resisting potentiality will the more readily disintegrate and succumb to the eroding process. Various experimenters have amply demonstrated that there are numerous ways in which this can be brought about. One illustration presents itself in the work of Rosenow, who postulated septic emboli settling as tiny nests in the depths of the tissue, progressing there into bundles of inflammatory islands, destroying the resistance of the local tissue and thus leading to ulceration. Other locally active factors can readily be supplied by vascular spasm, local spasmophilia of the muscles, irritating substances which are ingested and cause mucosal injury, and various other mechanical and chemical processes through which injury to the tissue may occur. Frequently gastric ulcers arise in association with foreign bodies, such as bezoars. Furthermore, ulcers are rather common complications arising in conjunction with diaphragmatic hernia at the point of maximal mucosal irritation. They present good examples of the ulcers arising mainly from local trauma to tissues. Single insults to tissue from whatever cause undoubtedly can produce disturbances which may cause symptoms and serious complications. No doubt hemorrhage or even perforation can be the result of single attacks on gastro-intestinal tissue. Chronic ulcer, however, is rarely the result solely of such trauma. The acute lesions heal rapidly unless some perpetuating factor of persisting injury to tissue comes into play.

Areal inflammatory lesions, mucosal erosions and acute ulcers probably can result from local insult to tissue, but they most likely

represent only one of the causes, or one of the stages, of chronic ulcer. For the completed accomplishment of chronic ulcer they need assistance from other factors which keep the original lesions from healing.

Factor of Aggression and Defense.—The only common denominator which is consistently and readily applicable to the lesions is that they occur in tissues bathed by the acid gastric chyme. When tissues other than those naturally accustomed to the chemical and mechanical action of gastric juice are exposed to the aggression of the acid chyme, the potentiality for ulceration promptly develops. Obviously, certain factors must arise which change either the resistance of the tissues to the eroding action of the peptic juice or the nature of the chyme so as to heighten its eroding potentialities. It is also evident that the change of balance is not permanent or invariably active in the same degree, because alternation of healing and activity is one of the inherent characteristics of the lesions. In many instances the ulcerating process terminates spontaneously, leaving only a scar to bear witness to the fact that anything unusual has occurred in the area. During the usual normal physiologic cycle the factors of aggression included in the eroding potentialities of the acid gastric chyme are amply counteracted by gastroduodenal tissues which satisfactorily protect themselves against this digestive action. So long as the balance between the defense of tissue and the aggression of acid chyme is properly maintained, nothing unusual happens. If one tips the scales, however, by heightening for a considerable period the factor of aggression or destroys in some way the mechanism of defense, it is conceivable that erosion of tissue will take place. Physiologists have amply demonstrated the increased vulnerability of tissues to the eroding action of the gastric chyme which has greatly accentuated acid-pepsin values. The more successful they are in obtaining acid chyme free from intragastric or extragastric diluents, the surer they are of producing erosions and ulcers in tissue exposed to these juices. They have furthermore demonstrated that tissues unaccustomed in their normal physiologic existence to the eroding actions of the acid chyme will succumb more surely and quickly.

The resistance of the jejunum, ileum and colon to the chemical action of undiluted gastric juice decreases progressively from the jejunum to the colon. It is of significance that factors of aggression which in themselves are inadequate to produce ulcers when tissues are naturally protected are capable of producing ulcers in tissues not usually so protected.

If trauma were caused by infected emboli, vascular spasm or mechanical irritation of the tissue which, normally is amply resistant to the acid factor of aggression, or if these eroding potentialities were intensified for a considerable period by oversecretion or underdilution, the physiologic requirement for the development of ulcer would seem

to be completed. Certainly these factors would produce ulcer in animals, and there is no reason to assume that any other result would obtain in man. These factors of aggression and resistance are applicable in the case of esophageal ulcer; with increased vulnerability of tissue, as by the infection and the regurgitation of acid chyme, erosion may easily occur there. Similarly, the peptic ulcers occurring about heterotopic gastric tissues, such as are occasionally demonstrable in the vicinity of Meckel's diverticulum, are practically always found in contiguous regions that are called on to resist the full aggression and irritation of the secretory products of these tissues. Since the tissues are not intended by nature to counteract the aggression of these secretory irritants, they seem to succumb more easily to chemical insults of this type.

Systemic Factor.—It is possible to produce in experimental animals physiochemical abnormalities which can readily be applied to the problem of peptic ulcer in man. Substantial corroborative evidence of the importance of the two factors just considered are available from experimental laboratories. There are, however, certain biologic phenomena to which man alone is heir. It has been observed that during periods in which the general health of patients has been undermined, the liability to development or recurrence of peptic ulcer seems to be appreciably accentuated. Frequently, with improvement in general health, there is less difficulty in controlling the symptoms, and the ulcer progresses rapidly to a quiescent state. In reviewing the histories of patients with peptic ulcer, it is not uncommon to find that the origin of symptoms occurred during periods of diminished resistance, and frequently the patients have noted that periods of reactivation correspond exactly to periods during which they were in the throes of some acute infection. The application of a yardstick to measure physical characteristics in the patients prone to the development of ulcer has not been very successful, because the factor of greatest importance seems to be one which is more psychophysiologic than physical and which can be measured anatomically and physically with great difficulty. Moreover, this factor seems to be fluctuating rather than constant. The syndrome of ulcer is characterized by periodicity and intermittency, and many chronic ulcers advance to complete cicatrization and healing; obviously, therefore, the factors which are at one time capable of producing and activating the lesions finally may cease to exert their influence and allow the ulcer to go on to quiescence or even to complete and permanent healing.

The characteristics so often duplicated in cases of peptic ulcer seem especially noticeable in cases of duodenal or anastomotic ulcer. There is a striking uniformity of temperament, but even more striking is the

similarity of mental and nervous reactions. Whether to consider these responses physiologic or psychologic seems of no great ultimate importance, since the two types are inseparable and in the end are probably cause and effect in reversible possibilities. The behavior and reactions of the patients are similar, and they conduct their affairs with like dispatch. They are unusually alert, attentive and keen, and frequently appear a bit stimulated, often resembling patients with moderate hyperthyroidism. They are ambitious, intensive, driving and high-strung. They are usually introspective, sanguine, suspicious, sensitive and given to periods of worry and depression. They are persistent in their activities, relentless in the pursuit of their objectives and forgetful of their physical requirements when they are busy with their occupational routine. They are likely to carry on despite obstacles until nervously and physically exhausted. Because of their persistence and ambition, they are frequently successful in their activities. They are, as a rule, willing to accept unusual responsibilities and often live persistently in an environment conducive to the development of great mental tension. The liability for the development of peptic ulcer among persons who live rather intensive lives is suggested by the incidence of the lesions in a series of two hundred specialists in medicine. Almost 20 per cent of the specialists were found to have peptic ulcers, practically all of which were duodenal; at least an additional 20 per cent admitted taking alkalis at intervals, especially during periods when they were unusually busy and overworked, in an attempt to keep up with their usual activities. These facts become increasingly interesting and significant in comparing the incidence of ulcer in this group with the incidence among two hundred Negroes living in a county-seat in central Texas. Negroes of all types were deliberately chosen for this group; most of them, of course, still represented the slow-moving, easy-going type, untouched by aspiration for culture. No instance of ulcer complicated by perforation, obstruction or hemorrhage was encountered. In only one instance was there sufficient evidence in the history to make a diagnosis of peptic ulcer. Incidentally, this instance occurred in a fretful, nervous, worrying Negro whose wife confided that he was constantly worrying about himself, taking medicine and complaining. Three per cent of the entire group had indigestion which was intensified late after meals, but in no other way did the history suggest the presence of peptic ulcer. Each Negro was questioned regarding his work, education, responsibilities, food and habits. In most instances, the actual living conditions were investigated. The diet of the Negroes was not balanced, and their habits almost invariably included the abuse of tobacco and alcohol. They dissipated recklessly. Their hours of sleep were entirely without regularity. They ate whenever they could and whatever they could get, and they lived under pathetic hygienic conditions; yet the syndrome

of chronic peptic ulcer was encountered rarely among them. They were to a great extent without work, and although many of them, even those with large families, scarcely knew the source of the next day's food, they usually seemed surprisingly unconcerned and laughed and jested about their difficulties.

The intricacy of modern life, with its ever-increasing rapidity of progress, exacts a toll in the health of those who choose to run in its race. Throughout the various strata of society there has always existed a certain sprinkling of persons who possess characteristics which are often reduplicated by patients having the syndrome of peptic ulcer. There seems to be a slightly greater tendency to find them among the better educated, more ambitious and more intensive members of society. Their abilities and their willingness to accept responsibility naturally increase the complexity of their lives far beyond that of those who follow along unperturbedly so long as others guarantee a more or less comfortable existence. Occasionally, there will arise in the life of a person, regardless of his position in society, troubles and periods of nervous or physical exhaustion during which he may be more liable to the development of peptic ulcer. Ordinarily his wants are limited, and his life is relatively simple. During the last decade, however, standards, especially in America, changed. Opportunity went recklessly about, knocking at every one's door. Success, as measured in terms of acquired wealth, was everywhere in evidence. American business crowded to the limit the resourcefulness of those connected with it. Increasing speed and efficiency became the American motto. Modern inventions came to the assistance of those who demanded more time-saving devices. Competitive requirements became more intricate, and better, keener and more intensive methods were necessary for those who sought to succeed. All America became prosperous. Barbers, butlers and ditch-diggers rubbed elbows with financiers in the offices of their brokers. Unfortunately, all this speed and hurry and recklessness developed a momentum and a pace which eventually was bound to produce a nation of nervously and physically exhausted persons. Then came the catastrophic behavior of the stock market, the period of precipitous deflation and the economic depression, and promptly a period developed in which there was much maladjustment. In the wake of all this intoxicating orgy were many persons for whom it became an actual struggle to survive. It is not difficult to understand that such a decade might well produce the heightened susceptibility of an increased number of persons to diseases which can be influenced by nervous and mental trauma.

Curiously enough, the desirable virtues of the modern, intensive, aggressive American, the characteristics which have been eulogized and designated as the cardinal marks of American successes, are precisely

the characteristics so often reduplicated in the ulcerous type of patient. Because a premium is paid for these characteristics, an ever-increasing number of persons will acquire them. Consequently, one may expect an increase in diseases having their origin in deranged nervous systems, and undoubtedly peptic ulcer is one of these diseases.

The periodicity and intermittency of symptoms in cases of ulcer frequently are determined by the variability of psychophysiologic influences incident to daily experiences of the patient. During periods of great emotional strain and of prolonged and unrelieved worry, and during long periods of mental or physical fatigue or of strain subsequent to catastrophes of any sort, symptoms are likely to originate or to reestablish themselves.

The rapidity with which epigastric pain with characteristics of peptic ulcer develops following an unexpected catastrophe is often remarkable. It has been a consistent experience of physicians treating ulcer that it is most difficult to accomplish the cessation of the manifestations of the lesion if patients continue working under tension or if they are constantly disturbed, worried and restless while under a regimen for ulcer in a hospital.

It has been pointed out that occasionally patients who present a syndrome suggestive of peptic ulcer do not have peptic ulcers.⁴² These patients are of the same type as those who are likely to have ulcer. Furthermore, it has been shown that just as symptoms of ulcer frequently reestablish themselves during periods of stress, so is the pseudo-syndrome also likely to arise under similar psychophysiologic disturbances. There is further similarity in the analogy in that, just as in cases of uncomplicated peptic ulcer the symptoms usually become readily controllable when the patient ceases active work, evades responsibility and takes a vacation, so also does the pseudo-ulcer syndrome usually disappear promptly even with the prospect of a pleasant holiday.

The pertinent analogy between these syndromes and the type of patients who experience them and their general behavior extending into the minutest details of symptoms suggests that the disturbance which is at the root of the entire syndrome is identical in both instances, and that this crucial derangement is in the nervous system. Factors which seem capable of influencing periodic reactivation of ulcer, which can prevent the healing of ulcerous lesions and which at times are entirely capable of bringing forth symptoms mimicking the apparent ulcer syndrome, although there are no demonstrable lesions detectable on exposed gastroduodenal tissues, must be of pertinent significance in the cause of the syndromes. The variability of the degree and of the intensity

42. Rivers, A. B., and Vanzant, F. R.: Peptic Ulcer Syndrome Without Ulcer, *Nebraska M. J.* **17**:465 (Nov.) 1932.

of these psychophysiologic tendencies probably represents the fluctuant which determines whether or not and when the syndromes will arise.

It is conceivable that, when ulcer is absent or when the defense reactions of the tissue are normally intact, a syndrome similar to that experienced without ulcer and entirely dependent on the disturbed neurogenic factors may develop. With the return of normal nervous reactions the balance is quickly reestablished, and the symptoms disappear. In the event of prolonged persistence of nervous hyperirritability and consequent accentuation of the aggressive factor, or in the presence of increased vulnerability of gastric or duodenal tissues, it is suggested that ulcer may easily be the final result. Quiescence or activity of the ulcer syndrome could be an alternating condition dependent on fluctuating psychophysiology with its resultant mechanical and chemical gastrointestinal alterations. Marked elevation of the acid-pepsin values is often noted during periods of excitement and tension, and it may be that one of the mechanisms of reactivation during these periods is related directly to chemical conditions affected by the nervous system in this manner.

CLINICAL APPLICATIONS OF VARIOUS HYPOTHESES

The three factors which thus stand out prominently from an analysis of various hypotheses applicable to the problem of ulcer in man are: (1) local trauma to tissue, (2) resistance of tissue to the aggression of acid gastric chyme and (3) systemic conditions. But it is not a matter of choosing which of these three includes the most logical causes for the formation of ulcer, because such lesions are probably the result of the combined interaction of the various factors. A graphic representation of these factors lending themselves jointly to the production of a composite picture of ulcer can be effected by the erection of a triangle (fig. 1).

Although each of these factors, as represented in figure 1, may be capable of producing ulcer, it is suggested that an interaction of several or all probably represents the more common formula; furthermore, in all probability the interaction of the various factors probably influences the course of the entire life cycle of the ulcer.

The many factors instrumental in causing peptic ulcer undoubtedly are of varying significance in different cases, and it is probable that the behavior of the lesions is influenced by fluctuations even in the same case. No inflexible and invariable constant will apply to the problem of the cause of ulcer in man; now one factor, now another assumes the position of major importance. It is, therefore, necessary to make an individual problem of each case of peptic ulcer.

Factor of Trauma to Tissue.—There are certain instances in which the trauma to tissues obviously overshadows other factors in etiologic

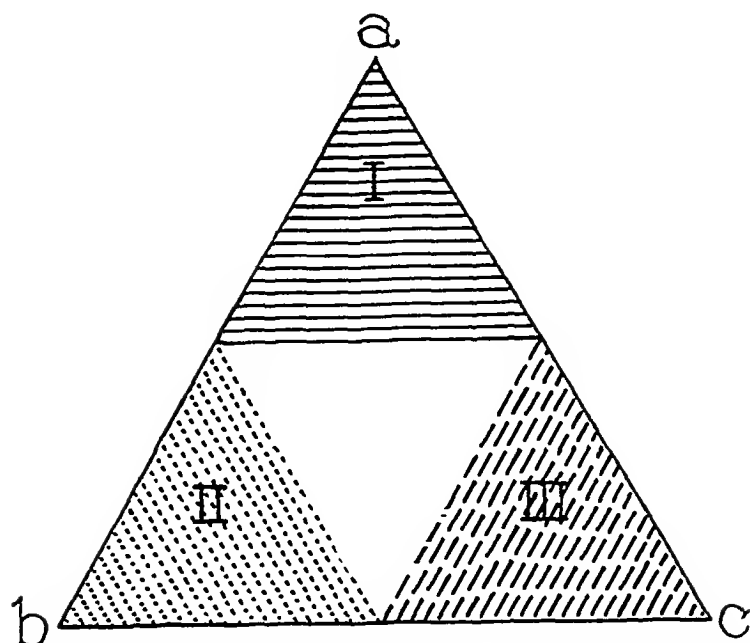


Fig. 1.—Triangle represents a diagrammatic scheme for the completed formula of chronic ulcer. It is constructed of three smaller triangles, indicated as triangles *I*, *II* and *III*. Each of the triangles lends two of its sides and their included angle to the formation of the larger triangle. Triangle *I* represents the factor of trauma to tissue; triangle *II*, the defense against aggression, and triangle *III*, the systemic factor.

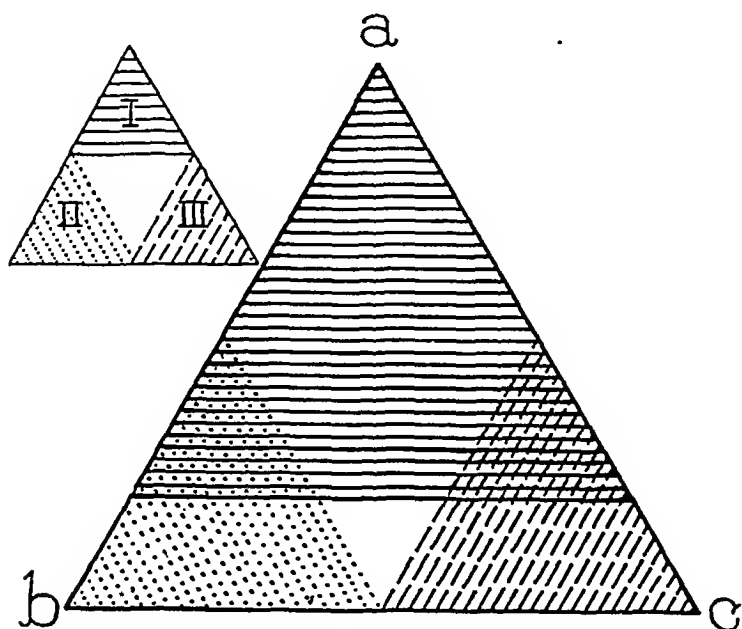


Fig. 2.—The base line of triangle *I* is pushed further into the larger triangle until it occupies almost the entire larger figure. This factor overshadows in importance the several other factors in the production of ulcer.

importance (fig. 2). It is not to be assumed that other factors do not enter to a varying degree into the production of peptic ulcers or into the course of the activity. It is intimated that in certain instances trauma to tissue seems to play a primary part in the onset and the course of the lesions. Such local injury to tissue is illustrated by the following cases:

CASE 1.—A girl, aged 5 years, shortly before coming to the Mayo Clinic, had an attack of acute tonsillitis. Several days after the onset she became weak, vomited large amounts of blood and passed tarry stools. Roentgenograms at the clinic gave evidence of duodenal deformity which was assumed to be due to an ulcer in that region. The infection was probably primarily responsible for the development of the hemorrhage. The tonsils were removed, and there has been no recurrence of the gastro-intestinal hemorrhages.

CASE 2.—A man, aged 34, had indigestion intermittently for ten years. There were six or eight episodes during which he complained of symptoms suggestive of peptic ulcer. With each episode he had hemorrhages, in the form of either melena or hematemesis. Between the attacks he was well. Roentgen investigation showed no evidence of deformity of the stomach or of the duodenum. Operation disclosed a small area of redness surrounded by considerable stippling in the duodenum. A diagnosis of areal duodenitis was made. Two dental roots were taken out, and material from them was injected into animals. In all of the animals hemorrhagic areas developed promptly throughout the upper part of the duodenum and about the pylorus. There has been no recurrence of the hemorrhages. It is assumed that the infection from the roots of the teeth may have been responsible for the inflammatory condition in the duodenum.

CASE 3.—A woman, aged 49, had epigastric pain and vomiting. At intervals during twelve years she complained of indigestion characterized by much vomiting and abdominal distention. Curtailing the amount of food promptly brought about improvement of the symptoms. In the last three or four years she had noted occasionally a burning sensation in the epigastrium, which was relieved by the ingestion of small amounts of food. On a few occasions there had been severe epigastric pain. Occasionally a small amount of blood was noted in the vomitus. Roentgenograms revealed the presence of esophageal diaphragmatic hernia with gastric ulcer; this was confirmed by exploration. The hernia was repaired. Nothing was done to the ulcer because it was assumed that it was due to traumatic erosion of the mucous membrane, the result of marked incarceration and angulation of the stomach in the thorax. The hernia was reduced, and seven months afterward roentgenograms revealed complete healing of the ulcer. It is obvious that local trauma to tissues incident to the presence of the diaphragmatic hernia was responsible for the ulcer.

CASE 4.—A woman, aged 33, presented herself at the clinic because of an abdominal tumor which had been detected two months previously and because she had lost strength and weight. At the time of examination the tumor was about 8 cm. in diameter. It was freely movable and not especially tender. Cramps had developed in the upper part of the abdomen two weeks prior to admission to the clinic. Occasionally there had been nausea and vomiting shortly after meals. Roentgenograms gave evidence of a large ulcer on the lesser curvature of the stomach. Exploration revealed the presence of a gastric ulcer and a large intragastric mass, which consisted of a ball of hair. This was removed. On the assumption that the ulcer was due to trauma from the foreign body, nothing was done to it. The patient recovered uneventfully and has remained well.

These illustrative cases seem to adduce evidence to suggest that local changes in tissue, whether due to infection, mechanical irritations or other trauma, can become in certain instances the chief causes of gastroduodenal lesions. This does not mean that other factors, such as the eroding action of peptic juice, do not in some way contribute to the ulcerating process. It suggests, however, that in the absence of such trauma the lesions would probably not have developed (fig. 3).

PREDOMINANCE OF FACTOR OF DEFENSE OF TISSUES AGAINST
AGGRESSION OF ACID

Careful evaluation of the available data occasionally suggests that in aggression of acid and defense of tissue lies the chief cause of peptic ulcer and of the maintenance of its chronicity. Physiologists seem to have demonstrated experimentally that this factor alone can

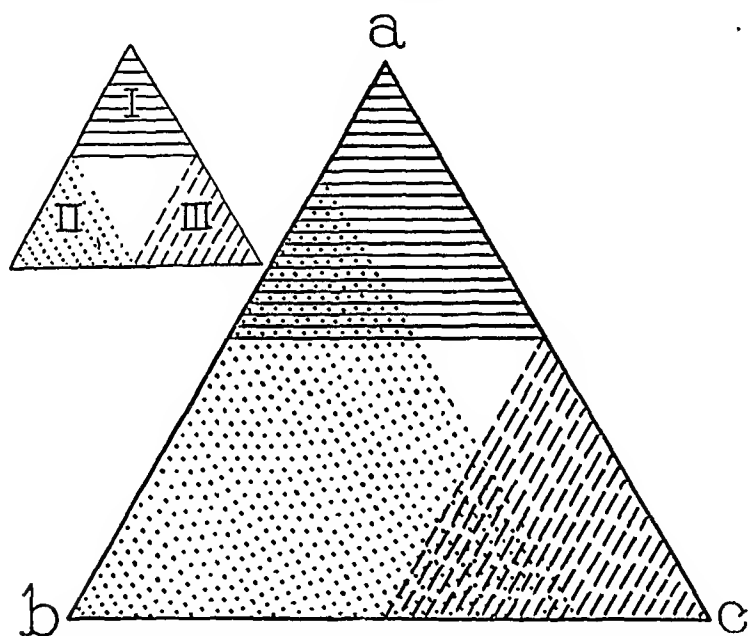


Fig. 3.—Diagrammatic representation of the predominance of the factor of defense against aggression of acid in the causation of ulcer. Triangle II has shifted its base line to include the major portion of triangle *abc*.

adequately accomplish the formation of chronic ulcer in animals. In certain instances such experiments find analogies in man. Certain patients seem to possess gastric mechanisms which maintain chyme of tremendously high concentration of acid, and pepsin values are often grossly accentuated. Furthermore, these patients frequently sustain high levels of acidity for unusually long periods after various stimulating influences have been applied to the gastric secretory mechanism. Increased liability to the formation of ulcer can readily be assumed in such cases, particularly in the presence of traumatized gastric, duodenal or jejunal tissues. Experiments with animals have further demonstrated that the impinging of highly acid chyme on tissues unaccustomed to the bathing influence of such chyme made them liable to the develop-

ment of ulcer. Similar conditions at times arise in man. The surgeon may have erroneously attached the ileum to the stomach on the assumption that he was making a gastrojejunostomy to cure duodenal ulcer. If the gastro-ileostomy functions satisfactorily, thereby effectively draining the major portion of the acid gastric chyme into the ileum, a gastro-ileac ulcer is almost certain to develop. The increased liability of patients to the development of gastrojejunal ulcers in the presence of retained high gastric acidity following gastro-enterostomy furnishes a further corollary to the experimentally produced chronic ulcers of Mann and Dragstedt. In such instances the factor of aggression as inherent in the high acid values possesses increased vulnerability because it is impinged on jejunal or ileac tissues which by nature are endowed with

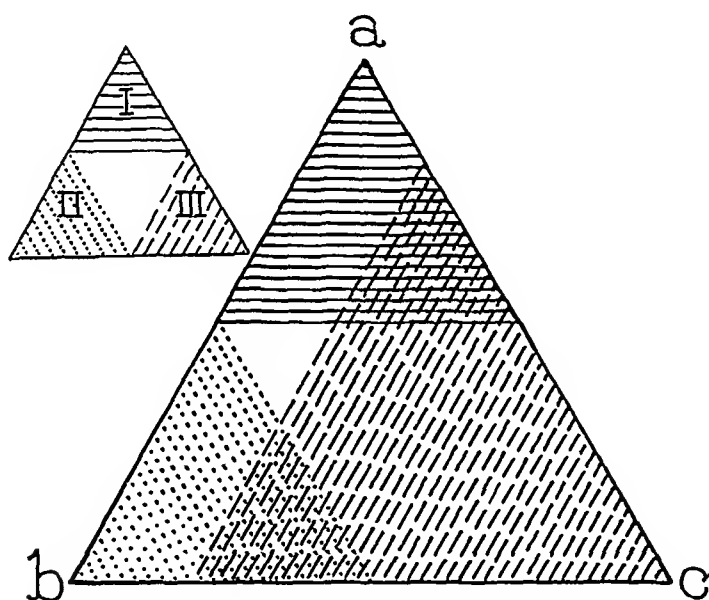


Fig. 4.—Predominance of the systemic influence in the causation of peptic ulcer. In this instance, triangle *III* has shifted its base line until it overshadows the other triangles included in triangle *abc*.

less efficient protecting mechanisms than are shown by the first portion of the duodenum, which is usually able successfully to withstand prolonged trauma by highly acid gastric juice. Case histories illustrating these factors follow:

CASE 5.—A man, aged 46, came to the clinic complaining of indigestion. Characteristics typical of ulcer dated back to childhood. Between the ages of 20 and 35, he had a great deal of difficulty in controlling the symptoms. At the age of 40 and again at 45, the difficulty had increased. Roentgenograms gave evidence of a duodenal deformity which was assumed to be duodenal ulcer. Results of the histamine test gave values as follows: The first specimen showed 106 total acid, 88 free hydrochloric acid, and 1,520 units of pepsin (normally below 500 units); the second specimen, 108 total acid, 94 free hydrochloric acid and 1,520 units of pepsin; a third specimen, 110 total acid, 96 free hydrochloric

acid and 1,680 units of pepsin; a fourth specimen, 126 total acid, 100 free hydrochloric acid and 2,840 units of pepsin; a fifth specimen, 136 total acid, 102 free hydrochloric acid and 2,360 units of pepsin, and a sixth specimen, 148 total acid, 106 free hydrochloric acid and 1,560 units of pepsin. Posterior gastro-enterostomy was performed; three weeks afterward another estimation of the histamine was made; the maximal total acid was 104, and the free hydrochloric acid, 98. Pepsin at this time was estimated to be 2,620 units. Obviously, in this case the factor of greatest potential danger for the reformation of ulcer rests in the tremendous aggression of acid and pepsin.

CASE 6.—A man, aged 24, entered the clinic in the spring of 1932, complaining of indigestion; characteristics typical of ulcer were present. Roentgenograms gave evidence of duodenal deformity, and operation was advised. An ulcer on the anterior wall of the duodenum was excised, one on the posterior wall was cauterized, and a pyloroplasty was made. Shortly afterward there was definite evidence of recurring ulceration beyond the pylorus with the formation of a crater. The estimation of gastric acidity after the use of histamine showed the following values: 86 free hydrochloric acid, 100 total acid; 118 free hydrochloric acid, 92 total acid; 120 free hydrochloric acid, 96 total acid; 104 free hydrochloric acid, 84 total acid; 104 free hydrochloric acid, 82 total acid, and 96 free hydrochloric acid, 74 total acid. Estimation of pepsin made on the specimen with the highest acidity showed 2,700 units. The ulcer on the posterior wall was then excised, and a gastroduodenostomy was made. Two weeks following this, gastric acidity was 104 total, and 98 free hydrochloric acid. In this specimen 1,900 units of pepsin was recovered.

Apparently the greatest problem in prevention of further difficulty in this case would have to be directed toward regulation of gastric chemistry, because the potentiality for the formation of ulcer under these conditions would be very high. The intimate mechanism responsible for the markedly attenuated ferment and acid values noted in cases 5 and 6 cannot be accurately ascertained. I have frequently noted, however, that in cases of peptic ulcers there seems to be a marked tendency for oversecretion of acid and attenuated values for pepsin. Stimulating test meals will often produce sustained curves of elevated values for acid and pepsin for much longer periods when ulcer is not present, and it may be that the instances of formation of ulcer and its maintenance rest with the persistence of the factor of attenuated aggression inherent in the acid pepsin.

CASE 7.—A man, aged 35, presented himself at the clinic because of abdominal pain. One year prior to admission, cholecystectomy was performed, and six months after this, gastro-enterostomy because of a duodenal deformity which was assumed to be ulcer. Shortly afterward, severe abdominal pain had appeared at irregular intervals. Nausea and vomiting followed the ingestion of all types of foods, and frequently acid gastric contents were regurgitated. There were periodic epigastric pain and, frequently, pain in the lower part of the abdomen, often associated with diarrhea. The patient had lost from 20 to 30 pounds (9 to 13.6 Kg.). Roentgenograms revealed the presence of a small ulcer just below the gastro-enteric stoma. Estimation of gastric acidity showed slightly elevated total and free hydrochloric acid. At operation an ulcer was found opposite an anastomosis made between the stomach and the lower part of the ileum.

Experiments on animals disclose that when the lower part of the small bowel is exposed to the traumatizing influence of acid chyme, it is likely to cause ulceration. Apparently the same condition obtains in man. Unfortunately, in this case

the gastro-ileostomy worked so well that most of the gastric content was deposited through the stoma and only a small amount by the pyloric route. It is not surprising that a gastro-ileac ulcer developed in this case.

CASE 8.—A girl, aged 9 years, was brought to the clinic because of intervals of pain in the region of the umbilicus which sometimes radiated to the right or left groin. Dark, tarry stools had been noted at intervals, usually three or four days after the onset of the pains. There was definite evidence of secondary anemia. Estimation of the gastric contents showed values of 40 for total and 24 for free hydrochloric acid. At exploration an ulcer was found at the juncture of the ileum and at Meckel's diverticulum, where the contents of the diverticulum impinged on the ileac wall. Examination of the submucosa of the Meckel's diverticulum revealed the presence of heterotopic gastric tissues.

In discussing ulcer of Meckel's diverticulum, Lindau and Wulff⁴³ stated that islands of heterotopic gastric mucosa similar histologically to that in the fundus of the stomach have almost invariably been found in these cases. Matthews and Dragstedt reproduced a counterpart of the ulcer of Meckel's diverticulum in animals by implanting a small isolated pouch of gastric wall into the jejunum and the ileum. When the pouch was transplanted into the jejunum, jejunal ulcer developed in 85 per cent of the animals, whereas, when the acid gastric juice was led into the ileum, it developed in 100 per cent.

The daily observation of patients with peptic ulcer soon impresses one with the fact that in certain patients it is particularly difficult to reduce the values of acid and pepsin in the stomach. Whether this is due to a particularly active gastro-intestinal reflex, whether it is due to excessive irritability of the mechanism responsible for the pouring of secretions into the stomach or whether it is due to deficiency of the neutralizing mechanism is difficult to determine. The evaluation of these causative factors, applicable in cases of gastric ulcer, cannot fail to take cognizance of the fact that in these cases the factor of predominant importance seems to be the regulation of gastric chemism. The case histories herein recorded seem to illustrate the predominant significance of these chemical factors. Cure or prevention of further ulceration should include efforts to reduce materially the acid gastric constituent in patients with gastric ulcer.

PREDOMINANCE OF SYSTEMIC FACTORS

There are certain instances in which peptic lesions seem to bear a distinct relationship in their etiology and course to the general health of the patient. Debilitating diseases, such as prostatic disease, and many

43. Lindau, Arvid, and Wulff, Helge: The Peptic Genesis of Gastric and Duodenal Ulcer; Especially in the Light of Ulcers in Meckel's Diverticulum and the Postoperative Ulcers in the Jejunum, *Surg., Gynec. & Obst.* **53**:621 (Nov.) 1931.

other conditions, are not infrequently associated with peptic ulceration. Periods of general diminished resistance following or during the course of acute or chronic infections not infrequently tend in some way to render the gastroduodenal tissues more susceptible to ulceration or to reactivation of ulceration if it is already present. Patients commonly experience hemorrhages from peptic lesions during the course of an acute infection of the upper part of the respiratory tract. It is not difficult to postulate that under such conditions the local resistance of the gastroduodenal tissues might definitely be diminished. The fluctuating influences dependent on the nervous and mental reactions of the patients seem to be still more important. The increased liability to the development of peptic ulcer when activities are carried on under tremendous tension has been suggested. Careful questioning of patients harboring peptic ulcer frequently brings out the information that it was during periods of psychic disturbances that the syndrome of ulcer began. Often also periods of recurring difficulty are simultaneous with periods during which the patients were particularly worried or were engaged in work requiring unusual nervous tension. In fact, there are many instances in which the entire syndrome of ulcer seems to be related in its inception and termination to disturbances of the nervous system. Often it is extremely difficult to decide whether the reestablishment of symptoms when patients are known to have peptic ulcers is actually due to a reactivation of the ulcer, because the inception and the termination of the symptoms parallel so exactly and so abruptly the particularly disturbing experiences. Illustrative cases follow:

CASE 9.—A man, aged 22, came to the clinic complaining of indigestion. Typical symptoms of ulcer had been present for a year. He had married about fourteen months previously. His father had given him as a wedding gift a business with which he was only slightly acquainted. He had a great deal of worry incident to the business and many responsibilities incident to the state of life into which he had just entered. It was during this period that the symptoms of indigestion developed. Whenever the patient met a difficult situation which caused him considerable concern, indigestion developed. Total gastric acidity was 98, and free hydrochloric acid, 80. A roentgenogram disclosed duodenal ulcer.

CASE 10.—A man, aged 31, entered the clinic complaining of indigestion of three years' duration. He smoked and drank alcohol excessively. A duodenal ulcer was discovered, and gastro-enterostomy was performed. He was well for eighteen months afterward. Then his wife became ill, and he came with her to the clinic. He was much worried about her illness, and gastric symptoms with definite characteristics of ulcer promptly developed. Later his son became ill and died, and the gastric symptoms recurred. During the following year occasional attacks of indigestion were invariably brought on by worry. Reexamination at the clinic revealed the presence of a gastrojejunal ulcer.

CASE 11.—A man, aged 73, came to the clinic because of prostate trouble. On reviewing the history, it was noted that during his youth he had had indigestion for four or five years. Roentgenograms of the upper part of the gastro-

intestinal tract disclosed evidence of an old duodenal scar. Since there had been no indigestion for thirty or forty years, the patient was closely questioned regarding the treatment which had cured the ulcer. He answered that the symptoms seemed to disappear. As a young man he had lived on a farm. He had married in his early twenties, moved to town and for several years conducted a small business with satisfactory financial results. He then decided to prepare himself for the ministry and moved to a larger city to attend school. Shortly afterward, his first child was born. He soon found that he had not saved enough money to live on. He also learned that his theologic course would take much longer than he had planned. This meant that he had to work at night to earn money; his wife also had to help. After another year their second child was born. This increased responsibilities and difficulties materially. During this period of worry and struggle indigestion developed. The symptoms persisted for three or four years. Then, after settling himself in his ministerial activities in a small town, his life became less strenuous, and with the return of better social and financial conditions his gastric symptoms disappeared permanently.

CASE 12.—A man, aged 70, had had various operations to relieve symptoms of peptic ulcer. The fourth operation, in 1922, was partial resection of the stomach. Shortly before, he was greatly disturbed by the illness and death of his wife. During this period he had uncontrollable indigestion, with symptoms suggestive of penetrating peptic ulcer. In the years following the operation he lived at the home of his married daughter. Many unpleasant incidents arose, and his indigestion recurred. Finally, in 1930, at the age of 68, he married a woman much younger than himself; this resulted in further difficulties. After several months he divorced his wife; not, however, before severe signs of recurring gastrointestinal disturbances had developed. At the time of the examination at the clinic an ulcer was found at the anastomosis just distal to the stoma. Under stimulation of histamine on several occasions, titration revealed the presence of total acids ranging between 84 and 96, and free acids ranging between 68 and 80. The content of pepsin in the gastric juice was about five times the normal amount.

This last group of cases suggest the part played by the nervous system in the causation of gastric symptoms. The exact parallelism between psychic trauma with unusual nervous tension and causation or reactivation of symptoms is apparent. In case 11, there had been no symptoms of ulcer for about forty years. The syndrome in this case exactly paralleled a period in the patient's life when he was living under tremendous psychic disturbances. In case 12, as in many of the other cases, it is difficult to ascertain whether the factor of aggression of acid or the neurogenic factor is of greater significance. In all probability, the neurogenic factor is of significance only because it produces other conditions, such as markedly prolonged, persistent attenuation of the high values of acid and pepsin, and for this reason such patients are increasingly vulnerable to the development of peptic ulcer.

SUMMARY

An attempt has been made to apply some of the hypotheses advanced to explain the etiology of peptic ulcer to the clinical problems of ulcer in man. In all probability, peptic ulcer is the result of several interact-

ing and variable factors. Physiologists have demonstrated that the aggressive action of undiluted juice can, by its eroding potentialities, produce ulcer. It produces ulcer the more effectively when it impinges on tissues unaccustomed and unprotected by nature to receive them. It is suggested that this factor of aggression is the more likely to cause ulceration when the resistance of the tissues exposed is in some way lowered by trauma of any kind. Thus, an infected intestinal wall or mucosa injured by mechanical or chemical irritants might well succumb and disintegrate when a membrane with normal protecting mechanism would remain intact. Systemic factors, if conducive to the diminution of the resistance of tissues or if capable of producing prolonged or persistent accentuation of the factor of aggression in the acid chyme, might well increase the liability to the development of ulcer and its recurrence in such cases. There seems no doubt that the factors involved etiologically in the formation of ulcer vary in different subjects at different times. Consequently, every patient presents problems which must be studied carefully. Such study should reveal the particular factor or combination of factors which will obtain in each case, and correction of their factors should be expected to result efficiently when applied in the treatment of ulcer.

ANGINA PECTORIS

SOME CLINICAL CONSIDERATIONS, WITH SPECIAL REFERENCE TO PROGNOSIS

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The accuracy of studies on the prognosis of angina pectoris depends on two factors. In the first place, errors will naturally occur because of mistaken diagnoses. There are a great many types of distress or pain in the chest that are not anginal in character which are often confused with true angina pectoris. Second, the duration of life after the symptoms have developed will obviously depend on the care that is taken in ascertaining when the disease actually first manifested itself. Frequently patients date the onset at a time when an attack of severe pain in the chest occurred, but on questioning them directly as to the first time that they had this sort of distress, even in a mild form or on walking, one learns that the disease began 1 or more years previously. The duration of life after the onset of the disease would consequently be greater according to the latter than according to the former notation. With this in mind, 141 patients with angina pectoris who have died were studied. In each case the diagnosis was quite certain and one of us had questioned the patients with care as to the exact onset of symptoms.

There have been numerous studies on the prognosis of angina pectoris,¹ and in general they have shown that the duration of life after angina has developed is from 4 to 5 years. An attempt has been made here to investigate certain factors that might influence prognosis, and

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1. (a) Mackenzie, James: *Angina Pectoris*, New York, Oxford University Press, 1923. (b) Herrick, James B., and Nuzum, Frank R.: *Angina Pectoris: Clinical Experience with Two Hundred Cases*, J. A. M. A. **70**:67 (Jan. 12) 1918. (c) Kahn, Morris H., and Barsky, Joseph: *Angina Pectoris: A Clinical Analysis of Two Hundred Cases*, Ann. Int. Med. **2**:401 (Nov.) 1928. (d) White, Paul D., and Bland, Edward F.: *A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of 500 Cases of the Former Condition and of 200 of the Latter*, Am. Heart J. **7**:1 (Oct.) 1931.

to appraise their value. The influence of the blood pressure level, sex, age of onset, age at death of parents, electrocardiographic changes and the effect of recovery from an attack of coronary thrombosis were analyzed. Information differentiating these various factors and the rôles that they may play in prognosis is rather meager. This is particularly true with respect to the differences in angina pectoris that occur in the two sexes.

The cases included in this study were selected in the following manner: Only those were included in which the date of death was known. Cases of angina pectoris occurring in young people with rheumatic aortic valvular disease were excluded. Although they have typical attacks of angina and are liable to sudden death, they do not suffer from

TABLE 1.—*Essential Data of One Hundred and Forty-One Cases of Angina Pectoris*

	Men	Women
Sex distribution	111 cases, 78.8%	30 cases, 21.2%
Age at onset.....	56 years	58.1 years
Range	36 to 71 years	36 to 71 years
Duration of angina.....	4.6 years	4.5 years
Range	1 month to 23 yrs.	3 months to 13 yrs.
Age at death.....	60.7 years	62.7 years
Range	41 to 76 years	46 to 74 years
Blood pressure	149.2/89.2	190/102
Range	95/72 to 238/124	140/74 to 244/130
Patients with systolic pressure under 140.....	46	None
Age at death of parents:		
Male parent	66.4 years	69.4 years
Female parent	64.5 years	67.3 years
Age at death of parents of patients whose angina began before age of 50.....	66.7 years	61.5 years

disease of the coronary arteries and may live for many years; they form a separate group. Likewise, a few patients were excluded who had attacks precipitated by paroxysmal rapid heart action. Furthermore, patients first seen during an attack of coronary thrombosis were deliberately excluded, although most of them had antecedent angina, because it was felt that a distorted picture would be obtained. If such cases of acute coronary thrombosis with its high immediate mortality were included, the duration of life for angina would be unfavorably and unreasonably weighted. Notwithstanding this, many of the patients with angina considered in this review did subsequently have attacks of coronary thrombosis from which they recovered or to which they succumbed. The purpose of the study was to throw light on the natural progress of true Heberden's angina as it is met with in general practice, and not in the hospital wards. All the patients were seen at the office or in consultation at their homes, and represent a fair index of what occurs in the general population.

Among these 141 patients there were 111 men (78.8 per cent) and 30 women (21.2 per cent). (All the essential data are charted in tables 1, 2 and 3.) The average age of the men at the onset of angina was 56 years and of the women, 58.1 years. For men the range extended from 36 years to 71 years and for women from 36 years to 70 years. The average duration of the symptoms of angina pectoris was 4.6 years in the men and 4.5 years in the women in this series. The shortest duration among the men was 1 month and the longest was 23 years. For the women, the corresponding figures were 3 months and 13 years. The average age at death for the men was 60.7 years, and 62.7 years for the women. The youngest and the oldest of the former were 41 and 76

TABLE 2.—*Blood Pressure Readings of Patients with Angina Pectoris*

	Number of Cases	Blood Pressure	Duration of Angina, Years	Age at Death, Years
Patients with hypertension (men)	47	175 / 100.6	4.3	62.4
Patients with normal blood pressure (men).....	62	129 / 80.1	5.0	59.1
Onset of angina under age of 50 (men).....	22	138.4/ 77.7	7.2
Onset of angina over age of 50 (men).....	89	151.9/ 92.1	4.0
Onset of angina under age of 50 (women).....	4	176 / 101.5	6.2
Onset of angina over age of 50 (women).....	26	192.2/ 102	4.2
Duration of angina of over 5 years (men).....	35	148.4/ 87.8
Duration of angina of over 5 years (women).....	11	185.3/ 93.1
Duration of angina of 1 year or less (men).....	12	151.4/ 89.6
Duration of angina of 1 year or less (women)....	7	175.1/ 94.7
Angina at rest.....	55	161.7/ 95.6	5.6 (life) 2.9 duration of angina at rest	61.6 64.6
Cardiac failure during course of angina (men)...	15	160.5/ 96.5	5.4	64.6
Cardiac failure during course of angina (women)	6	200.3/ 103	6.1	61.3
Obesity	72	4.5	59.3
Normal weight	10	6.9	59.0
Normal electrocardiogram	20	145 / 85	5.9	56.3
Negative T ₁ or T ₁ and T ₂ (men).....	21	148.5/ 90.7	3.7	59.7
Positive T ₁ or T ₁ and T ₂ (men).....	51	146.3/ 88.0	4.9	59.2
Negative T ₁ or T ₁ and T ₂ (women).....	6	219.1/ 120.8	6.3	61.8
Positive T ₁ or T ₁ and T ₂ (women).....	5	167.6/ 97.6	6.2	59.8
Prolonged QRS	11	154 / 97.7	5.4	64.0
Prolonged PR	5	159 / 94	4.9	66.0
Low electromotive force.....	5	154.2/ 80	8.9	64.4

years, and of the latter, 46 and 74, respectively. These extremes are naturally applicable only to this series of cases. Both younger and older persons suffering from angina pectoris are met with in general practice; in fact, one of us treated a man aged 24 for an acute attack of coronary thrombosis who had angina pectoris for a few months preceding the former condition. He is not included here because he survived and is still living.

The blood pressure showed distinct differences in the two sexes, an observation which is not entirely in accord with the view of Kahn and Barsky,¹⁰ who stated that blood pressure readings were about the same in the two sexes. The average reading for 109 men was systolic, 149.2 millimeters of mercury and diastolic, 89.2 millimeters of mercury. The extremes were 95 systolic and 72 diastolic on the one hand and 238 systolic and 124 diastolic on the other (one patient with a lower systolic

pressure had a diastolic pressure of 150). The average reading for 30 women was systolic 190 and diastolic 102. The extremes were systolic 244 to 140, and diastolic 130 to 74. It follows that women have much more hypertension with angina pectoris than men, the average difference being about 41 mm. for the systolic pressure and 13 mm. for the diastolic. What is of more clinical importance is that, whereas there were 46 men with angina pectoris with systolic pressure readings under 140, there was no woman with such a reading. In fact, there were only 2 with a pressure between 140 and 150; in one of these this reading was obtained during the height of an acute coronary thrombosis, and in the other it was present after an attack of the same nature. We have had occasion to utilize this feature with profit in cases of pain in the chest among women with low blood pressure in whom we suspected angina pectoris and in whom it was subsequently proved not to be present. One should therefore hesitate to make the diagnosis of angina pectoris unassociated with coronary thrombosis for any woman with a low blood pressure, especially for those under 50 years of age.

A comparison was made between patients who had hypertension and those who had normal pressure. In the first group, there were 47 with an average systolic pressure of 175 and a diastolic pressure of 100.6. The average duration of angina was 4.3 years. The average age at which these patients died was 62.4 years. On the other hand, there were 62 men with an average blood pressure of 129 systolic and 80.1 diastolic. The average duration of anginal symptoms was 5 years. The age at death in these patients with low blood pressure was 59.1 years. One may conclude therefore that in men with angina pectoris who have a low blood pressure the disease begins earlier in life, it lasts longer and the age at death is lower than in those with hypertension.

The effect of age at onset was analyzed to see whether there were any differences either in blood pressure or in the prognosis among those in whom the disease developed early in life. Of the 111 men, there were 22 in whom the angina began before the age of 50 years and 89 in whom it began after that age. The average blood pressure in the younger group was 138.4 systolic and 77.7 diastolic. In the older group the readings were: systolic, 151.9, and diastolic, 92.1. The duration of anginal symptoms was 7.2 years in the younger men and 4 years in the older. There were somewhat similar differences in the group of women. Of the 30 women, there were 4 under and 26 over 50 years of age at the time of onset of angina pectoris. The average blood pressure of the younger group was: systolic, 176, and diastolic, 101.5. The corresponding figures for the older group were 192.2 systolic and 102 diastolic. The duration of the disease was 6.2 years in the former and 4.2 years in the latter. It is clear that the younger persons with angina

pectoris, both men and women, have distinctly lower blood pressures, and that the duration of life is from 2 to 3 years longer than in the older.

An attempt was made to detect any distinguishing differences in the blood pressure in the short lived, as contrasted with the long lived, patients with angina pectoris. A group of 12 men and 7 women in whom the duration of angina was 1 year or less was contrasted with a second group of 35 men and 11 women in whom the disease lasted more than 5 years. No significant differences could be made out.

It is always a matter of interest whether attacks of angina occur only on effort or whether they are present even during rest. In fact, it has often been assumed that angina during rest is more ominous than angina on effort. A study was therefore made with this point in mind. There were 42 men and 13 women in whom attacks occurred not only on effort but also with varying frequency while they were at rest. In all the others, attacks were either entirely related to effort or occurred only rarely when the patients were at rest. A comparison of the blood pressure, the average age at onset of anginal symptoms and the average age at death showed no significant differences. The average duration of life after the onset of angina in this group was 5.6 years, which is even greater than for the entire series. The length of life after the anginal attacks began to occur during rest was 2.9 years. In more than half of the cases, attacks during rest appeared practically simultaneously with the onset of the disease. In a recent study by White,^{1a} it was found that 23 patients with angina of this severity died within 3 years, but 16 lived more than 7 years. It therefore follows that the duration of life after the onset of the disease is no shorter in cases of angina decubitus than it is in angina of effort.

Probably the most important etiologic factor in angina pectoris is heredity. It is difficult to obtain accurate data in this regard, because it requires knowledge of the diseases from which all the members of the various families suffer, which must be compared with similar data obtained in control cases. The information available in our cases was inadequate to warrant any such study. An analysis was made, however, of the age at death of the parents of the patients who had angina. The age at death of the male parent of the 68 men about whom there were data was 66.4 years and of the female parent, 64.5 years. The average age for the male parent of 12 women was 69.4 years and of the female parent 67.3 years. It is obvious that the age at death of the parents of the women with angina was about 3 years greater than that of the men. It is curious that the mothers of both the men and the women with angina died at an age of 2 to 3 years less than that of the fathers. This is distinctly different from the situation that exists in the general population. Extensive statistics, especially those obtained by insurance companies, show that the average age of women at death is 2 years or

more greater than that of men. The fact that female parents of patients with angina pectoris died at an age from 2 to 3 years less than that of the male parents may be explained if it is supposed that female parents played a larger rôle than male parents in transmitting the defect of vascular vulnerability. If this were not true, one would have to find that the age at death of the female parents would be over 2 years greater rather than 2 years less than that of the male parents. This conception is further validated when an analysis is made of the 22 patients in whom angina began before they were 50 years, for the female parents died at the age of 61.5 years, whereas the male parents died at the age of 66.7 years, a difference of over 5 years. Additional evidence that the hereditary factor is important can be obtained by comparing the age at death of patients with angina whose parents lived to an average age of over 70 with those whose parents lived to an average age of under 60. There were 26 of the former with a parental average age of 76.5 years and an average age at death of the patients of 63.4 years. There were 19 of the latter, with corresponding ages of 52.1 years and 57.8 years. In other words, patients with angina who have long-lived ancestors live 5.6 years longer than those whose parents die at a younger age.

Not infrequently patients with angina pectoris are subjected to tonsillectomy on the basis that a focus of infection is directly or indirectly related to the production of the attacks. It has become the fashion to search for foci of infection and to ascribe to such foci the cause of many diseases. A review was therefore made, patients who had tonsils removed some time during their life being compared with those on whom tonsillectomy had not been performed. There were no significant differences in the blood pressure findings, the average age at onset of angina or the age at death in the two groups. It is therefore unreasonable to remove tonsils either for prevention or for treatment of angina pectoris.

The relation between angina pectoris and cardiac decompensation is of some interest. There is a current teaching that when congestive failure develops in a patient who is having anginal attacks, the attacks disappear. Although this does frequently occur, it is by no means invariable, for in this series there were 5 men and 1 woman in whom attacks were not only present during decompensation, but in some instances were more troublesome. There were 15 men and 6 women who showed physical evidence of congestive heart failure during the course of the angina. In 7 cases decompensation followed in the wake of an attack of coronary thrombosis. Although the number is small, the proportion of men to women (5:2) is distinctly less than for the entire group of cases (4:1). The effect of hypertension in producing congestive failure is suggested in this discrepancy as in other data that follow. The average blood pressure in the 15 men was: systolic, 160.5,

and diastolic, 96.5. The corresponding figures for the 6 women were systolic, 200.3 and diastolic, 103. These figures are distinctly higher than those for the entire group. The average duration of life after the onset of angina was 5.4 years for the men and 6.1 years for the women. The duration of life after decompensation developed was 2.7 years for the former, and 1.3 years for the latter. The age at death of the men was 64.6 years and of the women, 61.3 years. The figures indicate that hypertension makes it more likely that a patient with angina pectoris will have cardiac decompensation, but that the duration of life after the onset of angina will be a year or more longer than for those who do not have decompensation. The age at death of the men in the group was 4 years greater than in the average of the entire series.

The relation between the recovery from an attack of coronary thrombosis and the course of angina pectoris was also analyzed. There were 21 men and 3 women in this series who recovered from an attack of coronary thrombosis. The average age at the time of the first attack of coronary thrombosis for the men was 57.6 years, and for the women, 65 years. The average age at death of the former was 60.8 years and of the latter, 68.6 years. It would seem that the length of life after recovery from an attack of coronary thrombosis was from 3 to 3½ years, and that the women were apt to have such attacks later in life.

Obesity is generally regarded as being related to the development and progress of angina pectoris. A comparison was therefore made between patients with excess weight and those who were normal or underweight. There were 68 men and 14 women, whose weights were known. Of these, there were 60 men with an average excess weight of 26.9 pounds and 12 women with an average excess weight of 46 pounds. The average age at death of the obese group was 59.3 years for the men and 59 years for the women. There were 8 men and only 2 women whose weights were normal or subnormal. The age of these at death was 59 years. Although these data are crude, as the greatest weight was not determined and many patients had lost weight previously, they are in accord with our general impression that obesity is not a significant factor in the production of angina, but rather that it indicates the type of person in whom the disease is more prone to develop. If obesity were actually related to the causation of angina pectoris, one should expect that the obese would die at an earlier age than those who are not overweight. Such was not the case in this study.

In an attempt to throw light on any factor that might influence the prognosis of angina pectoris, the presence or absence of electrocardiographic abnormality naturally deserves consideration. There were 104 patients for whom electrographic tracings were taken. Of this group, 20 showed essentially normal curves. Their average blood pressure

readings were 145 systolic and 85 diastolic. The duration of the angina was 5.9 years and the average age at death was 56.3 years. Thus it would appear that the finding of a normal curve is not necessarily a good prognostic sign, since the age at death of patients with such curves was less than the average age of the entire series and of those having electrocardiographic abnormalities. The duration of the anginal symptoms, however, was about 1 year longer in cases with normal electrocardiograms than the average of the entire series.

The changes that were particularly analyzed were negativity of the T wave in lead I or leads I and II, spread of the QRS complex and initial ventricular complexes of low amplitude. There were 21 men with inversion of the T wave in lead I or leads I and II and 51 men with positive T waves in these leads. The blood pressure readings were practically the same in the two groups. The duration of angina was 3.7 years for those with negative T waves and 4.9 years for those with positive T waves. The age at death, however, was about the same in these two groups, averaging over 59 years. The finding of negative T waves, therefore, shortens the total duration of angina by a little more than 1 year. There were 6 women with negative T waves and 5 with positive T waves. The former group had a much higher blood pressure than the latter. The readings were 219.1 systolic and 120.8 diastolic as compared to 167.6 systolic and 97.6 diastolic. The duration of angina was the same, a little more than 6 years. The average age at death was 61.8 years for the group with negative T waves and 59.8 years for those with positive T waves. In general it may be said that negative T waves in lead I or leads I and II shorten the duration of angina pectoris in men a little more than a year. This finding does not affect the prognosis in women, probably because a negative wave in lead I is so often an accompaniment of hypertension.

In 11 patients with a prolonged QRS complex (0.1 second or more), the average blood pressure was: systolic 154 and diastolic 97.7. The duration of angina was 5.4 years, and the average age at death was 64 years. It is evident that such a finding had no unfavorable influence on the progress of the disease; in fact, the opposite was somewhat indicated. A similar statement can be made for 5 patients who showed distinct prolongation of the PR interval. There were only 5 patients who showed electrocardiograms with distinctly low amplitude of the QRS complexes in all leads. The average blood pressure was 154.2 systolic and 80 diastolic. The duration of angina was 8.9 years and the average age at death was 64.4 years. Here again an electrocardiographic finding that generally carries with it a particularly grave prognosis seemed to have no such significance in this small group, for their duration of life was longer than the average of the entire series. It is difficult to compare these data

with the study by Willius² on the prognosis of patients with negative T waves, as in his study the duration of life was not calculated from the onset of symptoms, but rather from the time the patients were first seen by him.

In patients who have angina pectoris, sudden and unexpected death is a frequent occurrence. In fact, when the diagnosis is accurately made, such an event is anticipated. The frequency of sudden death and the other types of fatality and the causes were therefore analyzed in this study. Information was obtained concerning the manner of death of 86 men and 18 women. By the term sudden death is meant that a patient who is doing well, generally ambulatory, and attending to some duties is stricken dead instantly. There were 43 such instances among the men, or 50 per cent, and 5 among the women, or 28 per cent. In addition, there were 26 (30 per cent) men and 7 (39 per cent) women who died of coronary thrombosis. There were 5 men (5.8 per cent)

TABLE 3.—*Causes of Death in One Hundred and Four Cases of Angina Pectoris*

Cause of Death	Males		Females	
	Number	Per Cent	Number	Per Cent
Sudden	43	50	5	28
Coronary thrombosis	26	30	7	39
Congestive heart failure.....	5	6	2	11
Miscellaneous (acute pulmonary edema, cerebral accidents, bronchopneumonia, cancer, etc.).....	12	14	4	22

and 2 women (11.0 per cent) who died of ordinary congestive heart failure. Among the men, 3 died of acute pulmonary edema and 4 of cerebral accident; the latter cases were instances of cerebral hemorrhage or cerebral embolus. The remainder died of miscellaneous causes, such as bronchopneumonia, cancer and similar conditions. It is apparent that about one half of the patients with angina pectoris died suddenly and unexpectedly. No doubt in many of these, coronary thrombosis was the cause of the sudden death. This is not invariably true, however, for we have seen patients of this type who, it was revealed on post-mortem examination, had atheroma of the coronary arteries but no thromboses. Approximately 30 per cent of the patients with angina died after manifesting clinical evidence of coronary thrombosis. Most of the remaining patients died as a result of some form of cardiovascular disease, such as congestive heart failure, acute pulmonary edema and cerebral accidents.

2. Willius, Frederick A.: *Electrocardiography and Prognosis*, Arch. Int. Med. 27:434 (Oct.) 1922.

SUMMARY

This study concerns 141 fatal cases of angina pectoris seen in consultation practice. They were selected only so far as the diagnosis was definite and the entire duration of the disease was known. Cases that were first seen during an attack of coronary thrombosis were excluded. The main factors which were studied were those that had some possible bearing on prognosis.

There were 111 men and 30 women, a ratio of approximately 4:1. The average age at onset for the men was 56 years and for the women, 58.1 years. The average duration of angina was 4.6 years for the former and 4.5 years for the latter. The extremes were from a few weeks to 23 years. The average age at death was 60.7 years for the men and 62.7 years for the women.

The blood pressure findings were different in the two sexes. The average reading for the men was 149.2 systolic and 89.2 diastolic. The corresponding figures for the women were 190 systolic and 102 diastolic. It is of considerable importance that although there were 46 men with a systolic reading under 140 mm., there were no women with such a reading. The rarity of normal or low blood pressure findings in women with angina pectoris is very helpful in diagnosis.

A comparison of patients with hypertension with those having normal blood pressure showed that in the latter group the disease begins about 4 years earlier and lasts a little longer, and that the age at death is about 3 years less.

In studying the effect of the age at the onset of angina, it was found that in those in whom the disease developed before the age of 50 the duration of life after the onset was 2.3 years longer than in those in whom the disease developed after the age of 50.

No significant differences in the blood pressure could be found in the group of patients who lived less than a year as contrasted with those who lived more than 5 years.

Cases of attacks of angina while the patients were at rest were compared with those in which the attacks occurred almost exclusively on effort. Contrary to expectation, it was found that the duration of life after the onset of the disease, the age at death and the blood pressure readings were not significantly different in the two groups.

Evidence was presented to show that the hereditary factor is of great importance. It was found that those patients whose parents lived to an average age of under 60 died 5.6 years earlier than the group whose parents lived to an average age of over 70. The data also indicated that the defect of vascular vulnerability is transmitted more prominently by the female than by the male parent.

There were no differences in the course of the disease in those patients who had had a tonsillectomy and in those whose tonsils had not been removed.

The relation between angina pectoris and cardiac decompensation was also analyzed. The former frequently did not disappear with the development of the latter. It was found that the presence of hypertension made it more likely that congestive failure would develop some time during the course of the angina. The duration of life, however, after the onset of angina, was a year longer in those in whom decompensation was present than in those in whom it was not. The great frequency of hypertension in women explains the more common occurrence of cardiac decompensation in this sex.

The effect of recovering from an attack of coronary thrombosis was considered. The length of life after such an attack was about 3.5 years in both sexes, but women developed such attacks 3.6 years later in life than men.

Obesity was not found to affect either the age at onset or the duration of the disease. We feel that obesity has no important direct relationship to angina pectoris but merely reflects the constitutional type that is more prone to the disease.

Of 104 patients for whom electrocardiograms were taken, 20 showed essentially normal curves. The duration of the disease was a year longer, but the patients died at an earlier age than did either the average of the entire series or those with abnormal tracings. The duration of life after the onset of angina was 1 year less in those with inverted T waves in lead I or leads I and II than in those without such changes. In a small number of instances showing other electrocardiographic changes, such as prolongation of the PR interval and QRS complex or QRS curves of distinctly low amplitude, the prognosis as to the duration of life was slightly better than for the entire series.

Approximately 50 per cent of the patients died suddenly. In addition, about 30 per cent died of coronary thrombosis. Many of the instant deaths in the former group no doubt were due to coronary thrombosis as well. Somewhat less than 10 per cent died of congestive heart failure. The remainder died of miscellaneous causes, such as cerebral hemorrhage, bronchopneumonia, cancer and similar conditions.

RELAPSES IN CHRONIC ULCERATIVE COLITIS

CAUSES AND PREVENTION

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The cyclic nature of biologic phenomena is by no means confined to normal physiologic processes. The occurrence of cycles in pathologic states is well illustrated by the tendency to remissions and exacerbations which is a characteristic of chronic ulcerative colitis. The joy of the patient and the enthusiasm of the physician at the successful treatment and termination of an attack must always be tempered by the sober realization that the condition may recur. Knowledge of the pathologic changes that take place in this disease leads to a clear understanding of the inherent tendency to recurrence. This analytic study was undertaken in an effort to throw light on the factors which determine the incidence of, or which actually precipitate, the exacerbations, with the hope that the knowledge thus gained will prove valuable in prophylaxis during the quiescent stage or during the period in which the disease is under control. Our attention has frequently been directed to the similarity between factors which initiate the first attack of this type of colitis and those associated with subsequent exacerbations of the disease.¹

The histories of 364 consecutive patients with chronic ulcerative colitis who registered at the Mayo Clinic in 1931 and 1932 were studied. Many of the patients had been observed at the clinic previously, so that detailed clinical notes of many years were available. In addition, a well organized system of correspondence afforded further information as to clinical progress after dismissal of the patients. Communications were received from almost all of the patients twice yearly, and in most cases more often. The nature of the study would, of course, exclude patients whose disease was continuous—of unremitting activity—and a few other patients in whose records insufficient data were available.

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* The work for this paper was done at the Mayo Foundation when the author was a special student in medicine.

1. Larson, L. M.: Predisposing Factors in the Etiology of Chronic Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. 6:241 (April 22) 1931.

In 232 cases there were sufficient data to warrant inclusion of the cases in this survey; 209 patients had received medical treatment, and 23 had been previously subjected to some type of short-circuiting operation on the bowel. In every case, diagnostic procedures included proctoscopy, cultures of stools, repeated examinations of stools for pathogenic bacteria and parasites, and roentgenologic study of the thorax and colon; the barium sulphate enema was omitted in the rare case in which it was contraindicated by marked rectal stricture.

The results of the analysis of 209 cases in which treatment had been medical form the basis of this report. Several points of interest concerning the cases in which surgical operation had been performed are also considered.

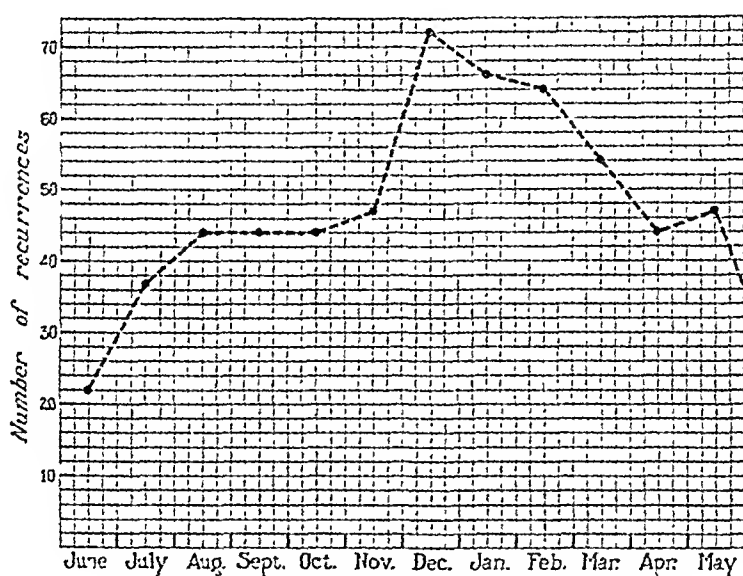
Concerning 276 of the recurrences involving 140 patients definite statements were available relative to the factor which immediately preceded or actually coincided with the beginning of the attack. Under the heading "infections of the upper part of the respiratory tract," which comprise 57 per cent of the total number of recurrences, are grouped colds, influenza, acute tonsillitis, sore throat and pneumonia. In the occasional case, respiratory infections ushered in each relapse. Over-exertion occurred in 19 instances (6.9 per cent), and nervous strain in 17 instances (6.2 per cent); specifically, these factors were manifested by fatigue, worry and emotional upset.

An appreciable number of relapses (12 per cent) were associated with conditions which traumatized or increased the irritability of the gastro-intestinal tract. These can be divided into the following classifications: dietary indiscretions, 14 instances (5.1 per cent); epidemic diarrhea, 10 instances (3.6 per cent), and intestinal trauma, 9 instances (3.3 per cent). The dietary indiscretions included overeating of foods high in roughage and gas-forming elements, alcoholism and excess in drinking of water during hot weather. Epidemic diarrhea, the drastic use of cathartics and various forms of manipulation of the bowel, such as proctoscopic examination and administration of barium enemas, irrigations with caustic solution and rectal surgical operations, accounted for the remainder of the attacks in this group.

In an attempt to eradicate every focus of infection, removal of infected tonsils and teeth had been common in the treatment of the patients, both at the clinic and elsewhere. A mild intestinal reaction, subsiding in from two to five days, was a common sequel, but in 14 cases (5.1 per cent) the operation initiated a prolonged recurrence of the ulcerative colitis.

In view of the fact that immunization, active or passive, or both, against diplostreptococcus of chronic ulcerative colitis was carried out

as a routine in the treatment of the patients, an infrequent cause of reactivation of quiescent colitis was the subcutaneous injection of sensitized vaccine. Nine episodes of this sort (3.3 per cent) occurred in 5 patients. The complete absence of recurrences following the use of the concentrated serum (antibody globulin solution) led to an investigation of the circumstances under which the vaccine had been given, since the former is used only at the Mayo Clinic, whereas the latter is given to each patient for administration by the family physician after dismissal. The exacerbation always occurred before the fourth injection of vaccine and usually following the first injection. Overdoses were common; 2 patients apparently became hypersensitive even to minute concentrations of the organism. In only 1 case did a relapse occur following an injection of vaccine at the clinic.



Monthly incidence of 586 recurrences.

Recurrence after abdominal operations were rare in this series. The 4 examples (1.3 per cent) were secondary to appendectomy. Instances in which patients had undergone from one to three major operations during periods of remission without ill effect only to have a severe exacerbation of the colitis initiated by removal of the tonsils or teeth were noteworthy.

In the miscellaneous group of 23 recurrences (8.2 per cent), 4 were associated with allergic manifestations; 3 were caused by attacks of hay fever, and 1 by sensitivity to ingested chicken meat. It is possible, of course, that allergic reactions enter into the etiology of recurrences more frequently than our histories would indicate. Some of the women with quiescent colitis went through pregnancy, delivery and the puerperium without unfavorable incident. In only 1 case did the gravid

state predispose to a return of symptoms; two successive pregnancies were thus complicated. Many women had noted increased intestinal activity and discomfort during the premenstrual phase. The remaining 17 relapses were preceded by acute exacerbations of chronic arthritis, severe bodily injuries, measles, chorea, erysipelas, dermatitis venenata or vaccination for smallpox.

An interesting fluctuation in the monthly incidence of relapses can be noted in the chart. Frequency of relapse was lowest in the summer months, and coincident with the increase in respiratory infections reached its peak in December, January and February. Of 586 exacerbations, involving 209 patients, 202 occurred in the winter, 102 in the summer, 146 in the spring and 136 in the autumn. In the individual case there was often a tendency for attacks to take place during the same month or season annually. In recurrences in the summer, although infections

TABLE 1.—*Relation of Age to Incidence of Recurrence in 165 Cases*

Decade of Life	Cases	Total Duration of Disease, Years	Number of Recurrences	Average*
10-19.....	16	87.5	60	0.69
20-29.....	51	256.0	157	0.61
30-39.....	51	311.5	155	0.50
40-49.....	24	172.0	74	0.43
50-59.....	18	126.0	50	0.40
60-69.....	5	34.0	14	0.41

* Average recurrences per year for each case.

of the upper part of the respiratory tract assumed lesser importance, dietary indiscretions (especially excessive intake of water), epidemic diarrhea and various other types of injury to the bowel represented almost half of the precipitating factors. The comparatively low incidence in summer in the entire series suggested a special study of cases from the southern states. Here the reverse finding was apparent, with the relapses in summer exceeding those in winter, but the relation between the season and the etiologic agent was analogous to that of the entire series. However, since the number of cases from southern states corresponded closely to the general geographic distribution of patients coming to the clinic, they were too few to warrant definite conclusions.

Table 1 includes data bearing on the correlation between the age of the patient and the frequency of recurrences. Only the cases in which definite and reliable information was obtained concerning both the total duration of the disease and the total number of distinct exacerbations after periods of quiescence were included. It will be seen that the frequency in the 165 cases decreased with each decade of life, so that in

the same period of time the patient of more than 40 years of age was likely to have only three-fifths as many relapses as the patient of less than 20 years. Chronic ulcerative colitis beginning when a patient is elderly runs a milder course. As one might suspect, the importance of the various precipitating factors for the different age groups fluctuated in an interesting way: During childhood and adolescence the part played by infections of the upper part of the respiratory tract was paramount, whereas during the third and fourth decades, the recurrences secondary to nervous strain, emotional shock, overexertion and dietary indiscretions increased markedly in frequency. The incidence of attacks was approximately the same for both sexes at various ages.

It might be assumed, on a theoretical basis, that the more extensive the involvement of the colon by the pathologic process, the more frequent would be the number of recurrences. By the use of proctoscopy

TABLE 2.—*Relation of the Extent and the Situation of the Lesion to the Number of Recurrences*

Extent of Lesion*	Cases	Total Duration of Disease, Years	Number of Recurrences	Average†
Rectum and sigmoid.....	58	312.0	155	0.50
Half of colon‡.....	30	158.5	83	0.52
Entire colon	56	348.5	185	0.53
Entire colon and terminal portion of ileum	21	168.0	87	0.52

* As determined by roentgenograms and proctoscope examination.

† Average recurrences per year for each case.

‡ Left half, 25 cases; right half, 5 cases.

and roentgenoscopy of the colon as a routine, it was possible to delineate the situation and boundaries of the lesion in each of the 165 cases in which there were data on the total duration and the total number of attacks. As shown in table 2, the situation and the extent of the disease bore no apparent relation to the incidence of recurrences. No single factor could be considered especially likely to induce reactivation of the process when situated in a particular part of the colon.

The foregoing analysis does not include the 23 cases in which previous treatment had been colostomy, cecostomy, appendicostomy, ileostomy or ileosigmoidostomy. The average interval since the operation was four and four-tenths years. In 21 of the 23 cases, the cyclic attacks of ulcerative colitis had continued with the same precipitating factors, in approximately the same ratio, as in the nonsurgical cases. Second or third operations (plastic repair following colostomy or ileostomy; ileostomy or ileosigmoidostomy, in cases in which cecostomy had previously been performed, and subtotal or total colectomy) were performed

on 11 patients of the group. The risk, judging by the mortality rate of the subsequent procedures, was tremendously increased over that of the primary operation. Bargaen, Brown and Rankin² emphasized the wisdom of confining the operation to the treatment of complications of the disease. Fifteen of the patients had marked stricture of the rectum, extensive polyposis of the colon, vesicosigmoid fistulas or a combination of these conditions. It is clear that even in cases in which treatment is surgical, the problem of recurrence of activity is important and that any guides in the prophylactic care will be valuable.

COMMENT

It may be that the facts elicited in a study of this kind have only relative value. The responsibility for distinguishing between a mild increase in intestinal activity and true exacerbations of the disease rests entirely with the individual investigator. Furthermore, unless he has had the opportunity to trace the patients personally from the inception of the disease through each of the successive exacerbations, with frequent notes on the temperature, body weight, daily number and character of the stools and the degree of anemia, it will be impossible to ascertain the actual duration, or to grade the severity, of the many attacks.

In the care of the patient with chronic ulcerative colitis, one must distinguish between clinical and pathologic activity. Once the disease has appeared, the normal characteristics of the mucous membrane and the other layers of the wall of the bowel are almost invariably permanently altered. Generalized contraction of the lumen is a constant feature, and often a thick-walled, stiff, straight tube remains. Healing of the severe destructive processes may result in the formation of multiple polyps or strictures of the rectum or the colon. With the advent of the first-named complication, the patient may notice, after a period of quiescence, the gradual return of bleeding, tenesmus and the greater frequency of stools. The amount of blood passed is usually out of proportion to the other symptoms. If the second complication develops, pockets of pus may accumulate proximal to the stricture in various parts of the colon, and by sudden discharge over a period of days may simulate a significant increase in pathologic activity.

Rectal stricture, consisting of localized regions of inflammatory tissue and scar tissue on a diffusely narrowed base, will interfere materially with the passage of the normal fecal current, so that the stools are smaller in size and are passed more frequently. Under these conditions,

2. Bargaen, J. A.; Brown, P. W., and Rankin, F. W.: Indications for and Technique of Ileostomy in Chronic Ulcerative Colitis, *Surg., Gynec. & Obst.* **55**: 196 (Aug.) 1932.

therefore, a portion of the patient's difficulties is undoubtedly mechanical, and it is not surprising that approximately a fourth of the patients who were to all intents well continued to have from two to five normal-appearing bowel movements daily over a period of years. Accordingly, in this group we have excluded from consideration as recurrences all exacerbations that did not last at least a month and in relation with which profound changes in the character and the number of the stools were not displayed.

The most important single incitant of recurrences—infections of the upper part of the respiratory tract—accounts for the high percentage of relapses in winter and is unfortunately most difficult to overcome. Although a climate which predisposes to such infections is prone to result in reactivations of the disease, a sojourn in warmer regions is not necessarily effective in preventing them. Apparently the patient carries his susceptibility to colds with him. An attempt to end the episodes by the removal of normal-appearing tonsils or tonsillar tags may be doomed to failure, and, as has been shown, may occasionally result in a severe recrudescence of the colitis. A history of repeated recurrences of colitis after respiratory infections may, however, in the occasional case, warrant removal of the tonsils, even in the absence of a history of acute tonsillitis.

It is generally considered sound practice to remove definitely infected tonsils and pulpless or periapically infected teeth, because a specific causative organism may be dormant, waiting for favorable circumstances or a change in its own life cycle to cause an exacerbation, or because a nonspecific focus of infection tends to undermine the normal defenses of the body.

In the summer, traumatization of the bowel in its broadest sense presents an important hazard which should lend itself to satisfactory control. Epidemic diarrhea, food poisoning, seasonably abundant and cheap, coarse-fibered vegetables and an inordinate excess in the intake of fluids serve individually or in combinations to render the colon susceptible to reactivation of the disease. At all times strenuous catharsis (especially before operation) and superfluous irrigations or irrigations with caustic solutions are to be avoided. If it is realized that the end-results of healing may cause clinical pseudo-activity after all of the pathologic activity has subsided, overtreatment of the colon by well-intentioned physicians will be reduced materially. Surgical manipulation of a rectum or colon already injured by the ravages of chronic ulcerative colitis is undertaken with a forbidding risk and should be confined to imperative measures such as simple drainage of an abscess. To accord conservative expectant treatment and cautious surgical operation at the optimal time are trustworthy principles.

The grouping of emotional and physical strains as predisposing factors of recurrences in the third and fourth decades of life is evidently a reflection of the economic and social stresses which are most active during that time. The psychoanalytic studies made by Murray³ in cases of chronic ulcerative colitis and the observations of numerous other investigators afford convincing evidence of the causal relationship of emotion to hypermotility, hypersecretion and spasticity of the colon. So far as possible, all stimuli which will upset the patient's nervous system are to be avoided. The patients soon gain a remarkable insight into their disease, so that minor setbacks have an unduly depressing effect on them. The physician must concern himself particularly with maintaining the patient's morale and helping him regain an optimistic view of the situation.

In using the diplostreptococcus vaccine during periods of quiescence, precautions against contamination or freezing are essential. By means of a carefully taken history and proper skin tests, hypersensitivity should be excluded, and the initial dose should not exceed 0.1 cc. of the vaccine, given subcutaneously. Increases must be gradual; systemic reactions are best avoided. At any signs of increased intestinal activity, a short period of rest followed by a reduced dose will be found advantageous.

Quiescent and adequately treated ulcerative colitis may be no contraindication to pregnancy or to necessary abdominal surgical operation.

Prominent among the prodromal symptoms when exacerbations are imminent are malaise, general exhaustion and fatigue, paresthesia of the abdominal wall, migratory pains in the flanks, aching joints and the appearance of superficial sores on the tongue and buccal mucous membrane. At such times, as well as during the premenstrual period, the prophylactic measures outlined deserve particular attention.

SUMMARY

Recurrences in a series of 209 medical and 23 surgical cases of chronic ulcerative colitis have been studied for predisposing and precipitating factors. Acute infections of the upper part of the respiratory tract initiated attacks in 57 per cent of the cases in which predisposing factors were recorded. Overexertion and emotional upsets were factors in 13 per cent; various conditions which traumatized or increased the irritability of the gastro-intestinal tract were factors in 12 per cent, and the removal of oral foci of infection was a factor in 5 per cent. The incidence of recurrences was lowest during the summer and reached its

3. Murray, C. D.: *Psychogenic Factors in the Etiology of Ulcerative Colitis and Bloody Diarrhea*, *Am. J. M. Sc.* **180**:239 (Aug.) 1930.

peak during the winter. A general relationship between the season and the etiologic agent is shown. Frequency of recurrences decreased with each decade of life. The situation and the extent of the lesion did not influence the frequency of recurrences. In cases in which a short-circuiting operation on the bowel had been made recurrences were common, and the relative importance of the precipitating agents was similar to that in cases in which treatment was medical. The distinction between clinical and pathologic activity is made. The prophylactic care of chronic ulcerative colitis in the quiescent stage is considered.

CORONARY THROMBOSIS

PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM

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Acquired perforation of the infarcted interventricular septum is a rare condition which is infrequently diagnosed. The only reported case in which an antemortem diagnosis was established is that of Brunn in 1923. The purpose of this report is to present another case of this complication of coronary thrombosis and to review the subject completely. I shall also attempt to present the criteria which make this condition, rare as it is, one that is clinically easily recognizable.

Krumbhaar and Crowell,¹ in 1925, gathered from the literature 654 cases of nontraumatic rupture of the heart, almost all secondary to coronary occlusion. At present the total is well over 700. From these figures it is evident that rupture of the heart is not rare. However, there are recorded only 17 cases of perforation of the infarcted interventricular septum, or nearly 3 per cent of all reported nontraumatic ruptures of the heart. With the addition of this case the total is brought to 18. The accompanying table lists all the cases recorded up to 1933. It will be seen that there were 13 men and 5 women affected; the ages were between 46 and 81 years, the average being 61.

Excluded from this series are all traumatic cases and ruptures caused by abscesses and parasitic cysts. All perforations at the base of the septum, which include congenital defects of the septum, rupture of congenital aneurysms of the undefended space and of the right aortic sinus of Valsalva, and ulcerative defects caused by bacterial endocarditis, are also excluded. This report deals only with the cases of coronary thrombosis which result in infarction of the septum and perforation.

REPORT OF A CASE

History.—I. A., a housewife, aged 60, admitted to the hospital on Dec. 21, 1932, for four years had arterial hypertension with a systolic pressure as high as 240 mm. of mercury. The family physician stated that during this period no

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*Eugene Meyer, Jr., Fellow in Pathology.

1. Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, *Am. J. M. Sc.* **170**:828 (Dec.) 1925.

Cases of Nontraumatic Rupture of the Heart, Recorded up to 1933

Case	Author	Age	Sex	Murmurs and Thrills	Location of Thrombosis	History Characteristic of Coronary Occlusion	Location of Rupture in the Septum	Size of the Rupture	Duration of Life in Days After Perforation	Comment on the Coronary Arteries
1. Latham ²(1)	61	M	Systolic thrill and rough murmur	Not noted	+	Posterior	Pin point	1	Atheromatous deposits
2. Latham ²(2)	60	M	Not noted	Not noted	+	Not indicated	Less than 2 in.	..	Arteriosclerosis with bony transformation
3. Belth ⁴	79	M	Not noted	Not noted	+	Middle	About 1½ in.	..	Arteriosclerosis with bony transformation
4. Peneock ⁵	62	M	Not noted	Not noted	±*	Lower half	Large	..	Arteriosclerosis with bony transformation
5. Pergami ⁶	60	M	Not noted	Not noted	+	Not indicated	Not described
6. Grosse ⁷	52	M	Not noted	Left anterior descending artery	+	Middle, anteriorly	2 em.	..	Not described
7. Youmans ⁸	52	F	Systolic thrill and blowing murmur	Not noted	+	Lower half	6 by 3 mm.	..	Left anterior descending artery occluded by a fibrous plaque
8. Brunn ⁹(1)	46	M	Systolic thrill and murmur, soft diastolic murmur	Left anterior descending artery	+	Lower half	3 by 1 em.	..	
9. Brunn ⁹(2)	52	M	Systolic thrill and diastolic murmur; short diastolic murmur	Right coronary and posterior descending arteries	+	Lower half	4 by 2 em.	..	Sclerotic narrowing of left anterior descending artery
10. Martin and Waugh ¹⁰	52	M	Systolic loud murmur	Not noted	+	Lower half	Jagged (1 by 3 em.)	10	"Obliterating endarteritis" of left anterior descending artery
11. Hyman ¹¹	52	M	Shrill systolic murmur	Left anterior descending artery	+	Lower half	Large	>1	Sclerosis of both coronary arteries
12. Freeman and Griffin ¹²	(1)	60	M	Systolic thrill and loud murmur	Examination incomplete	±*	Lower half	Finger tip	1	Marked sclerosis of both coronary arteries
13. Freeman and Griffin ¹²	(2)	70	F	Systolic thrill and loud murmur	Examination incomplete	+	Lower half	Match stick	2	Sclerosis of both coronary arteries
14. Rintelen ¹³	73	F	Systolic thrill and murmur	Left anterior descending artery	+	Lower half	Wide catheter	..	Sclerosis of both coronary arteries
15. Buccianti and Supino ¹⁴	70	F	Rough systolic thrill	Left anterior descending artery	+	Lower half	> 1 em.	..	
16. Benson et al. ¹⁵(1)	60	M	Not noted	Left anterior descending artery	±*	Posterior	2 em.	..	
17. Benson et al. ¹⁵(2)	81	M	Loud systolic murmur	Right coronary artery	+	Lower half	1 em.	..	Left coronary artery closed by an old thrombus
18. Sager	60	F	Systolic thrill and loud murmur	Left anterior descending artery	+	Lower half	Pin point	..	Narrowing of right coronary artery by sclerosis

cardiac murmurs were audible. Her last illness began five days before hospitalization, with constricting pain across the chest and syncope. There was constant substernal and epigastric boring pain radiating upward into the neck. She perspired profusely, while her body felt "hot and cold all over." She was dyspneic and orthopneic. The output of urine was diminished.

Physical Examination.—The patient was well developed, dyspneic and orthopneic, with grayish cyanosis of the skin, and was bathed in a cold sweat. The cervical veins were distended. Examination of the lungs gave negative results. The heart was enlarged to the left in the fifth intercostal space. There was a rough systolic precordial thrill and a loud harsh systolic murmur, both of which were maximal at about 4 cm. to the left of the sternum in the fourth and fifth intercostal spaces and were transmitted to the left axilla and to the back just beneath the left scapula. The second aortic sound was louder than the second pulmonic. The blood pressure was 165 systolic and 95 diastolic. The pulse was rapid and regular. The liver was palpable 3 cm. beneath the right costal margin; there was no edema of the ankles. The temperature was 100.4 F.

Laboratory Examination.—Examination of the blood revealed: hemoglobin (Sahli), 76 per cent; white blood cells, 14,000 per cubic millimeter, and polymorphonuclear leukocytes, 82 per cent. The venous pressure by the direct method was 18 cm. of water; the blood urea nitrogen, 36 mg., and the blood sugar during fasting, 360 mg. per hundred cubic centimeters. Examination of the urine showed a specific gravity of 1.032; sugar, 3.3 mg. per hundred cubic centimeters; no acetone; a slight trace of albumin. Microscopic examination revealed a few hyaline casts; the output was about 450 cc. daily. An electrocardiogram showed low voltage in all leads; the main deflection of the QRS complex inverted in lead I; the RT transition in all leads was off the baseline; the Q wave in lead III was not accentuated.

Clinical Diagnosis.—The condition was diagnosed as: essential hypertension; coronary sclerosis; acute coronary thrombosis; infarction and rupture of the interventricular septum, and diabetes mellitus.

Course.—The symptoms did not abate. On the day preceding the patient's death râles were heard throughout the entire field of the lungs. The blood pressure had dropped to 96 systolic and 72 diastolic. The skin was cold and clammy; the lips, cyanotic. The temperature had risen to 101.4 F. Death occurred in pulmonary edema five days after admission to the hospital.

Postmortem Examination (by Dr. Sager and Dr. Hitzig).—The anatomic diagnosis was: acute thrombosis of the anterior descending branch of the left coronary artery; marked arteriosclerotic narrowing of the posterior descending branch of the right coronary artery; acute myomalacia of the apex of the left ventricle, both left papillary muscles and the lower half of the interventricular septum, with perforation of the latter; parietal thrombosis of the left and right ventricles; hypertrophy and dilatation of both ventricles; localized pericardial adhesion; pulmonary edema; pulmonary emphysema; universal pleural adhesion; pulmonary arteriosclerosis; advanced arteriolosclerosis of the kidneys, and chronic passive congestion of the viscera.

Macroscopic Examination of the Heart: The heart weighed 500 Gm. The pericardium was smooth except over an area of about 4 cm. in diameter on the anterior surface of the left ventricle near the apex, where the pericardium was adherent but easily separated. The heart had a globular shape, and the apex was formed entirely by the left ventricle. The apical third of the left ventricle border-

ing on the interventricular septum anteriorly was soft and could be easily indented with the finger while the rest of the ventricle was firm. The right ventricle was markedly dilated and slightly hypertrophied. Within the apex of the right ventricle was an almond-shaped, grayish-red thrombus, which adhered to the columnae carneae and to the apical portion of the septum. Several of the columnae carneae in this region were greenish gray.

Saline solution poured through the aorta into the unopened left ventricle passed into the right ventricle through an opening hidden deeply between the



Fig. 1.—View of the right ventricle, showing the interventricular septum with a ureteral catheter in the septal defect.

columnae carneae at a point about 3 cm. above the apex of the ventricle. This opening would otherwise have been overlooked. After the left ventricle was opened, this aperture could also be seen by holding the heart up to the light (fig. 1).

The left ventricle was markedly hypertrophied but only slightly dilated. The apex and the lower half of the septum were relatively thin. The lower half of the septum was grayish green and necrotic, and bulged slightly to the right. A conical depression about 7 mm. in diameter was situated 3 cm. above the apex of the left ventricle; a ureteral catheter inserted into it passed upward, anteriorly and to the right, through the interventricular septum to reappear in the right ventricle at the point through which the saline solution had escaped (fig. 2). The lower

third of the left ventricle anteriorly and both papillary muscles were grayish green with hemorrhagic streaks. There were gray thrombi adherent to the endocardium in the region of the apex. The auricles and valves showed no pathologic changes.

The coronary ostia were patent. Both arteries showed extensive arteriosclerosis. The anterior descending branch of the left coronary artery was markedly narrowed by arteriosclerosis, and at a point 2.5 cm. distal to its origin was closed by a red thrombus which extended for a distance of 3 cm. The posterior descending branch of the right coronary artery was thickened by subintimal fatty deposits and was markedly narrowed. The aorta presented a marked degree of arteriosclerosis with calcification and ulceration of its thoracic and abdominal portions.

Microscopic Examination.—The myocardium of the anterior wall of the left ventricle where it joins the septum was necrotic. Nuclei were absent, and the

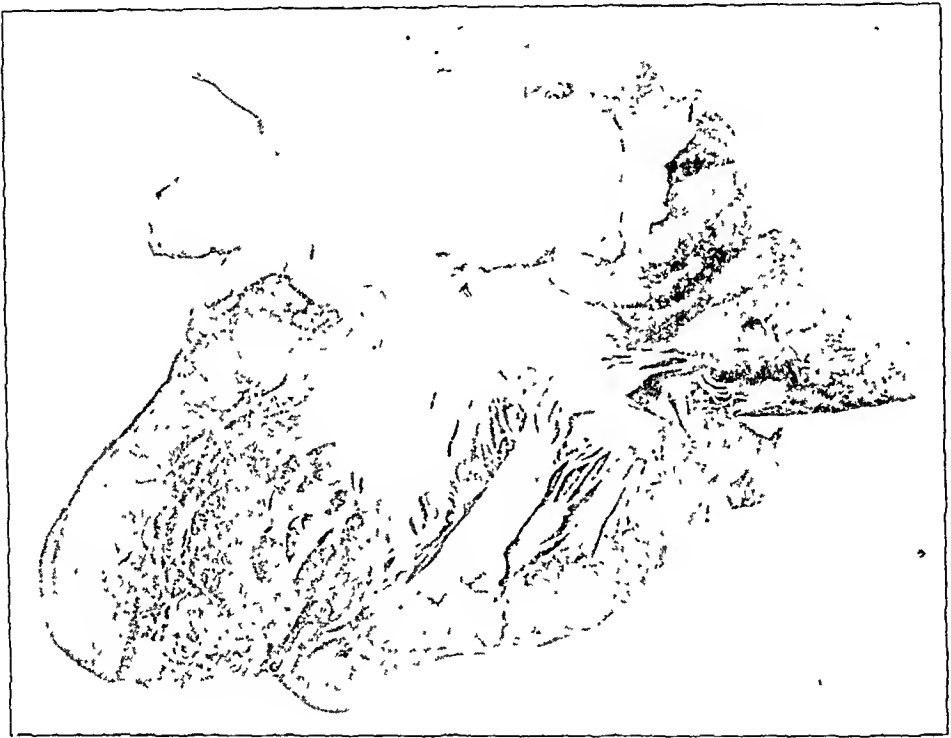


Fig. 2.—View of the left ventricle, showing the interventricular septum with a conical depression where the catheter enters the defect.

muscular striations not discernible; the "ghost" myocardium stained lightly and diffusely with eosin. There were bandlike infiltrations along the septums, consisting chiefly of polymorphonuclear leukocytes and macrophages. Toward the periphery of the section were numerous macrophages loaded with iron-containing pigment, and there were young fibroblasts invading the necrotic area.

The anterior descending branch of the left coronary artery revealed a thick intima composed of fibrous tissue with heavy deposits of fat and calcium. Much of the fat was doubly refracting. There was extensive new formation of elastica in the intima. The lumen was closed by a clot consisting of interlacing strands of fibrin with many enmeshed erythrocytes. Organization by fibroblasts had begun. The media was thinned out through much of its circumference. In the adventitia were small collections of lymphocytes. The posterior descending branch of the right coronary artery showed a similar process, but without thrombosis.

CASES IN THE LITERATURE

Latham² in his lectures on the heart, published in 1845, first reported rupture of the infarcted septum. In his first case he presented a description of the clinical phenomena, to which nothing can be added today. Unfortunately, in his case, as in many of the cases of disease of the coronary arteries described in the early literature, the examination of the coronary arteries for thrombosis was not done completely or was not completely recorded. However, it will be apparent from the typical history of occlusion of the coronary arteries and from the details of the postmortem examination that a thrombosis probably did exist. Libman³ has pointed out, however, that in certain cases myocardial infarction may occur without an acute coronary thrombosis. The patient was a man, aged 61, a corpulent gouty cripple. He suddenly experienced a severe constant pain which "occupied the entire front chest and passed along both clavicles to the top of the shoulders." On the third day of his illness he was given *vinum colchici*, on the fourth, the pain disappeared, but on the sixth it reappeared with aggravated severity: For the first time a systolic precordial murmur not transmitted to the arteries was heard. "He was deadly pale, and from the center to the extremities of the body he was cold as marble, and streaming with perspiration, but his pulse was of good strength. . . . I staid with him through the night, still giving at intervals opium and aether and ammonia, but all to no purpose." He died the next day. At necropsy although the rest of the myocardium seemed normal, "the septum was pale and soft, manifestly in consequence of fatty degeneration. In the septum at its posterior junction with the parietes there was an oblique rent passing through it from ventricle to ventricle. On the side of the left ventricle it was an inch and a half in length, on the side of the right it just opened at a point, so that the aperture was not at first noted from the right ventricle. The coronary arteries contained some atheromatous deposits, but were quite pervious."

Latham's second case was observed clinically by another physician; only the postmortem specimen was available to him. It was the heart of a man, aged 60, who had suffered from angina pectoris. Three days previous to his death he experienced an extraordinarily severe attack of substernal pain which was constant. A rupture of the septum was found. The coronary arteries were thickened and "contained bony matter deposited between the coats." Mr. Paget and Dr. Ormerod described the muscular tissue near the perforation as being "evidently disorganized, for it appeared as irregular granular cords without any transverse striae, which were elsewhere well marked."

The second report was that of Beith⁴ in 1850. A man, aged 79, fell, and for five days thereafter felt a constricting pain in the chest radiating to the back of the left shoulder. Death ensued. The heart weighed 17 ounces (481.9 Gm.). There was a dense ossifying obstruction of the anterior descending branch of the left coronary artery. Midway between the apex and the base of the interventricular septum was a rupture about 1½ inches in diameter, its edges covered with fibrin. Auscultatory details were not mentioned.

2. Latham, P. M.: *Lectures on Subjects Connected with Clinical Medicine Comprising Diseases of the Heart*, London, Longmans, Brown, Green and Longmans, 1845, vol. 2, p. 168.

3. Libman, E.: The Importance of Blood Examination in the Recognition of Thrombosis of the Coronary Arteries and Its Sequelae, *Am. Heart J.* **1**:121 (Oct.) 1925.

4. Beith: A Case of Septal Rupture, *Tr. Path. Soc. London* **3**:69, 1850.

Peacock,⁵ in 1854, demonstrated the heart of a man, aged 62, who had slight pain in the chest for four or five days. On the night of his death he began to breathe rapidly and hurried to bed. He denied that he was uncomfortable. No physical findings are mentioned. The heart weighed 14 ounces (396.9 Gm.). One third of the way from the apex to the base there was a large rupture of the interventricular septum. The myocardium about the rupture was flaccid. The coronary arteries were studded with atheroma and bone. The aortic valve was less capacious than normal.

Pergami,⁶ in 1876, reported the case of a man, aged 60, who died suddenly with terrifying *angor animi* and pain in the left side of the chest. A circular opening was found in the interventricular septum. It was larger on the left side of the septum than on the right. The myocardium about the defect was degenerated. The coronary arteries were not described.

The next case was described in 1906. Grosse⁷ studied the heart of a man, aged 52, who had been well until a year previous to his death, when he began to complain of precordial pain and dyspnea on exertion. After a long rest he felt sufficiently well to return to his work. His pain suddenly reappeared with great severity, and he became orthopneic. He was later taken to the hospital, but died before a satisfactory physical examination could be made. In the middle of the interventricular septum near the anterior ventricular wall was an oval defect 2 cm. in length with a thrombus attached to the edges. The anterior descending branch of the left coronary artery was narrowed throughout; 3 cm. below its origin it was obstructed by a thrombus 18 mm. in length.

In 1921 Youmans⁸ reviewed the literature on perforation at the base of the septum, but his own case belongs to the group here discussed. A woman, aged 52, had severe prolonged attacks of angina pectoris with dyspnea, orthopnea and edema of the feet for ten days before hospitalization. The heart sounds were regular and rapid. A precordial thrill was palpable, and there was a blowing precordial murmur difficult to time and loudest at the left of the sternum in the fourth and fifth intercostal spaces. At necropsy, an aneurysmal pouch in the left ventricle "antero-laterally to the right and opposite to the interventricular septum in its lower half" was found. A few centimeters above the apex was a defect in the interventricular septum, 6 by 3 mm., the edges being covered by an adherent thrombus. The surrounding myocardium was softened. The anterior descending branch of the left coronary artery was occluded by a fibrous plaque.

Brunn,⁹ in 1923, described 2 important cases in detail. The first case was that of a man, aged 46, who five days before hospitalization began to experience severe constant substernal pain with *angor animi*. His skin was gray and livid, and there was edema of the legs. The systolic blood pressure was 136. The heart borders were widened. Over the lower portion of the sternum and to the left in the fourth

5. Peacock: A Case of Rupture of the Septum, *Tr. Path. Soc. London* **5**:102, 1854.

6. Pergami, E.: *Ulcera perforante del setto del cuore: morte subitanea*, *Ann. univ. di med. e chir.* **237**:42, 1876.

7. Grosse, B. J.: *Ein Fall von Ruptur der Herzkammerscheidewand mit retrograder Emboli in der Leber*, *Inaug. Dissert.*, Rostock, C. Bolat, 1906; quoted by Rintelen.¹³

8. Youmans, J. B.: *Perforation of the Interventricular Septum of the Heart, with Report of a Case*, *Arch. Int. Med.* **28**:495 (Oct.) 1921.

9. Brunn, F.: *Zur Diagnostik der erworbenen Ruptur der Kammerscheidewand des Herzens*, *Wien. Arch. f. inn. Med.* **6**:533 (Oct.) 1923.

and fifth intercostal spaces a rough systolic thrill was palpable. A long systolic murmur was audible over the middle of the sternum; two days later a soft diastolic murmur developed in the same area. The liver was tender and palpable three fingerbreadths beneath the right costal margin. The patient died on the day following entrance to the hospital. The clinical diagnosis had been endocarditis with rupture of a papillary muscle. An aneurysmal pouching was found at the apex of the left ventricle. About 3 cm. above the apex there was a tear in the septum, 3 by 1 cm., surrounded by a considerable area of myomalacia. There was a fresh thrombus in the anterior descending branch of the left coronary artery.

Brunn's second case was that of a man, aged 52, who for a week had substernal pain radiating to the left arm and with it a sense of impending dissolution. His hands were cold and cyanotic. He was dyspneic and coughed up red sputum. The radial pulse on the right was small; on the left it was absent. Cardiac dullness was increased. A fine systolic thrill was felt and a rough systolic murmur heard over the lower part of the sternum. The liver was palpable below the costal margin. Four days later a short diastolic murmur appeared, all pulses disappeared, and shortly afterward the patient died. In view of Brunn's experience with the preceding case, he made a diagnosis of septal perforation with embolism of the subclavian and iliac arteries. At necropsy, myomalacia of the interventricular septum and the posterior wall of the left ventricle was found. There was a perforation of the septum, 4 by 2 cm., situated about 3 cm. above the apex. The left ventricle was hypertrophied. There was marked arteriosclerotic narrowing of the anterior descending branch of the left coronary artery and a thrombosis of the right coronary artery extending into its posterior descending branch. This is the only recorded case in which the antemortem diagnosis of perforation of the infarcted septum was proved.

In 1925 Martin and Waugh¹⁰ reported the case of a man, aged 52, who was suddenly seized with an attack of acute precordial pain. Examination of the heart shortly after the onset gave negative results, but on the following day a loud systolic precordial murmur was heard. He died in shock ten days after the onset. The left ventricle was hypertrophied. At the apex of the heart was a soft necrotic aneurysmal bulge. About 3 cm. above the apex in the softened septum was a star-shaped perforation. "Obliterating endarteritis" of the anterior descending branch of the coronary artery was reported.

Hyman,¹¹ in 1929, presented the case of a man, 52 years of age, in whom a sudden onset of severe abdominal pain suggested the diagnosis of ruptured peptic ulcer. The heart sounds were feeble. He was cold, clammy and pulseless. Four hours later a shrill systolic murmur was heard over the precordium. Spontaneous rupture of the heart was suggested, but the site of rupture was not localized. The electrocardiogram revealed abnormal R T transitions in leads I and II with inversion of the T waves in all leads; the Q wave in lead III was not deep. A perforation of the interventricular septum was found near the apex. Both coronary arteries were sclerotic; there was a thrombus occluding the anterior descending branch of the left coronary artery.

Freeman and Griffin,¹² in 1932, added 2 cases. Their first case was that of a man, aged 60, who was hospitalized because of dyspnea and cyanosis. No cardiac

10. Martin, C. F., and Waugh, T. R.: Rupture of the Septum Ventriculorum, *Ann. Clin. Med.* 4:183 (Sept.) 1925.

11. Hyman, A. S.: Spontaneous Rupture of the Heart; Perforation of the Interventricular Septum, *Ann. Int. Med.* 3:800 (Feb.) 1930.

12. Freeman, W., and Griffin, E. D.: Cardiac Rupture with Perforation of the Interventricular Septum, *Am. Heart J.* 7:732 (Aug.) 1932.

murmurs were heard. His blood pressure was 102 systolic and 68 diastolic. The patient later went into shock, becoming pale, cold and clammy. A systolic thrill was felt, and a loud systolic murmur was audible over the entire precordium. The pulse was absent at both wrists; the liver was palpable two fingerbreadths beneath the costal margin. The electrocardiogram showed abnormal R T transitions in all leads, and inverted T waves in lead I. The Q waves in lead III were not deep. Leukocytosis was present. A diagnosis of "acute aortic stenosis," ruptured aortic leaflet or dissecting aneurysm was made. At necropsy the left ventricle was seen to be hypertrophied. There was a perforation about 1 cm. in diameter in the interventricular septum near the apex. There was severe arteriosclerosis of both coronary arteries with almost complete obliteration of the anterior descending branch of the left coronary artery. (The coronary arteries were not completely dissected in order to preserve the specimen for museum purposes.)

Their second case was that of a woman, aged 70, who was suddenly seized with severe abdominal pain radiating to the left arm and scapula. On admission, except for a state of shock and slight edema of the ankles, the cardiac status was negative. The electrocardiogram suggested coronary thrombosis. On the fourth day a loud systolic murmur and a marked thrill appeared. The blood pressure was 150 systolic and 60 diastolic. She died on the fifth day. The diagnosis made was acute coronary thrombosis. The interventricular septum was pale and soft with hemorrhagic areas; there was a perforation admitting a match 2 cm. above the apex. The coronary arteries were sclerotic, but the "location of the thrombus was not further investigated."

In 1932 Rintelen¹³ reported the case of a woman, 73 years of age, who had complained of slight cardiac pain for many years. She suddenly felt weak, vomited and became dyspneic and cyanotic. Her heart was enlarged to the left and right. Over the entire precordium a thrill was felt and a murmur heard which was transmitted to the aortic area, where the second sound was absent. The second pulmonic sound was audible. She died within a few hours after hospitalization. The diagnosis was aortic stenosis. Postmortem examination revealed the left ventricle to be hypertrophied. There was a septal defect admitting a wide metal catheter 3 cm. above the apex of the left ventricle. The tissue about the rupture was hemorrhagic and fatty. Microscopic section showed necrosis of the myocardium. The anterior descending branch of the left coronary artery, 3.5 cm. from its origin, was narrowed and ulcerated by an arteriosclerotic process, and the lumen at this point was closed by a grayish-red thrombus.

Buccianti and Supino¹⁴ also reported their case in 1932. A woman, aged 70, complained of pain in the upper part of the abdomen for several months. Shortly before her hospitalization the pain became excruciating. Cardiac decompensation was evident; the lips were cyanotic, the skin pale and the ankles edematous; the patient was dyspneic. The blood pressure was 155 systolic and 90 diastolic. The liver was palpable three fingerbreadths below the right costal margin. The heart was enlarged. There was a rough systolic precordial thrill and a rough systolic murmur within the apex replacing the first sound and obliterating the second. The R T transition was abnormal in lead II; the T wave was negative; the Q R S complex was low in lead I; there were nodal rhythm and atrioventricular dissociation. The Q wave in lead III was not deep. On the basis of the electrocardio-

13. Rintelen, F.: Zur Kenntnis des myomalazischen Septumdefektes und zur Spontanruptur des Herzens, *Ztschr. f. Kreislaufforsch.* **24**:375 (June 15) 1932.

14. Buccianti, E., and Supino, L.: Considerazione cliniche e anatomo-patologiche sull'infarto del miocardio, *Clin. med. ital.* **63**:1085, 1932.

gram, a diagnosis of coronary thrombosis with infarction of the interventricular septum was made. At necropsy an apical fibrous aneurysm of the left ventricle was found. About 4 cm. above the apex was a perforation in the septum less than 1 cm. in diameter. The anterior descending branch of the left coronary artery was calcified and thrombosed. No lesion was found in the junctional tissues to account for the atrioventricular block.

Benson, Hunter and Manlove,¹⁵ in 1933, noted 2 cases of interventricular defect among 40 cases of rupture of the heart. The first case (case 33) was that of a man, aged 60, who was found dead in bed. There was a hemorrhagic adhesion of the pericardium to the posterior interventricular sulcus. The posterior paraseptal regions of the right and left ventricles and the septum itself were the seat of a hemorrhagic infarction with a ragged rupture 2 cm. in length in the posterior portion of the septum. The coronary orifices were patent. The branches of the left coronary artery were narrowed, and the left circumflex was blocked by an old white recanalized thrombus. The right coronary artery was closed by a fresh thrombus 2.5 cm. in length. The authors made a pathologic diagnosis of "septic infarct," "fresh thrombosis of the right coronary artery" and "probably syphilitic arteritis." By "septic infarct" they probably referred to the streaklike polymorphonuclear infiltrations commonly seen in myocardial infarcts, for they did not mention the finding of bacteria. Since the aorta was free from syphilis and the coronary orifices were patent, it is hardly likely that syphilis played any part in this case.

In the second case (case 34), a man, aged 81, had complained of pain in the upper part of the abdomen and in the right side of the chest for three years. Ten days before his death he became pale and dyspneic. Eight days later, on hospitalization, his heart was found to be enlarged 13 cm. to the left of the sternum. A loud systolic murmur was heard best over the mitral area and was transmitted to the axilla and to the back. The liver was three fingerbreadths beneath the costal margin. The blood pressure was 140 systolic and 70 diastolic. Four hours before death he went into a state of shock. The presence or absence of thrills was not mentioned. At necropsy a hemorrhagic pericarditis was found. The apex of the left ventricle was thin-walled. In the distal half of the muscular septum was a ragged rent 1 cm. in length. The anterior descending branch of the left coronary artery was occluded by a fairly recent reddish thrombus with recanalization. Microscopic examination at the edges of the rupture showed that "it had existed long enough to give rise to granulation tissue."

Faulkner, Marble and White¹⁶ made statistical mention of a case of coronary thrombosis with rupture of the interventricular septum, but gave no details. Their case, therefore, has not been listed in the table.

COMMENT ON THE CLINICOPATHOLOGIC SYNDROME

In reviewing the cases presenting more complete clinical data, one notes that while the patients' symptoms are typical of acute coronary thrombosis, the cardiac signs are identical with those of congenital patency of the interventricular septum. In the face of such a coincidence,

15. Benson, R. L.; Hunter, W. C., and Manlove, C. H.: Spontaneous Rupture of the Heart, *Am. J. Path.* 9:295 (May) 1933.

16. Faulkner, J. M.; Marble, H. C., and White, P. D.: The Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, *J. A. M. A.* 83:2080 (Dec. 27) 1924.

therefore, one is justified in assuming that a rupture of the infarcted septum has taken place. Application of this principle in the case here reported made it possible to predict the results of the postmortem examination. Of the cases in the literature, adequate clinical description is presented only in the following: Latham, (first case), Brunn, (both cases), Martin and Waugh, Hyman, Freeman and Griffin, (both cases), Rintelen, Bucciatti and Supino, and Benson, Hunter and Manlove (second case). In all these cases the physical findings simulate closely those associated with Roger's disease. In rupture of the infarcted septum the defect is relatively small. On the principle that the smaller the aperture the louder is the murmur and the rougher the thrill, we must, therefore, expect the cardiac signs to be well marked even when the patient is moribund. On the other hand, in congenital patency, in which the septal opening is not infrequently very large, the typical murmurs may be absent.

Congenital defects are consistent with longevity while acquired defects are not, because in the latter the patients die of the myocardial infarction and not of the perforation. The small opening in the septum, although it gives rise to intense murmurs, does not seriously affect cardiac dynamics. One never sees the deep cyanosis of the later stages of congenital patency in acquired septal perforation, because the relative differences in pressure in the ventricular chambers are maintained even though the individual pressures are changed; furthermore, the clinical picture is usually attended by signs of shock; and the small defect, in any case, would hardly allow sufficient blood to pass from the right to the left ventricle to produce deep cyanosis.

One who has occasion to observe a case from the onset of the coronary occlusion before perforation has ensued, is impressed by the sudden appearance of the forceful thrill and murmurs which later signalize the perforation. Such was the experience of Latham (first case), Martin and Waugh, Hyman and Freeman and Griffin (both cases). In the case here reported the family physician gave assurance that the murmur and thrill were never heard before. However, one does not need this foreknowledge to make the diagnosis of perforation of the infarcted septum; the physical signs in conjunction with the clinical history are quite sufficient.

The symptoms and the general physical appearance of the patient are the same as those in myocardial infarction without perforation. There are moderate fever and leukocytosis. One observes the familiar signs of shock: grayish cyanosis, cold clammy skin and a small pulse. To these signs may be added various degrees of left cardiac failure, as shown by orthopnea, paroxysmal dyspnea and pulmonary edema, and sometimes of right cardiac failure, manifest by a deeper grade of cyanosis, an enlarged liver, peripheral edema, distended veins and an

elevated venous pressure. The blood pressure is low, or, if formerly high, becomes lower. The physical signs may include a pericardial friction rub, feeble quality of cardiac sounds and an enlargement which is usually referable to the effects of previous hypertension rather than to recent dilatation of the heart. In addition to these one finds the physical signs of Roger's disease. In typical cases a harsh systolic murmur and a rough systolic thrill are established over the precordium with their maximum intensity to the left of the sternum in the fourth and fifth intercostal spaces. The murmur is usually transmitted to the left axilla and subscapular region, but not to the great vessels. In the present case, the murmur was maximal farther to the left than usual, perhaps because of the marked hypertrophy of the left ventricle with a more transverse position of the heart. When the diameter of the defect in the septum enlarges to 2 cm, or more, a diastolic murmur may also be heard.

The electrocardiogram is typical of acute coronary artery occlusion. However, none of the cases of septal perforation in which the electrocardiogram is recorded shows the deep Q wave in lead III which has been regarded by some as characteristic of infarction of the septum.

At necropsy, the lower part of the interventricular septum is found infarcted to a greater or lesser degree, as is the adjacent anterior or posterior wall of the left ventricle and a small area of the right ventricular wall. In almost all cases on complete examination the cause of the infarction is found to be a thrombotic occlusion of the coronary arteries. Usually the anterior descending branch of the left coronary artery is thrombosed, while the posterior descending branch of the right is severely narrowed by arteriosclerosis. In the second case of Brunn and the first of Benson and his co-workers, the reverse situation existed—the posterior descendens (or the right coronary artery, as in the latter case) was thrombotic, and the anterior descendens was narrowed by arteriosclerosis. The infrequency of rupture of the septum when compared to rupture of the anterior and posterior walls of the left ventricle is explained by the rich anastomotic arterial supply of the septum, well demonstrated by Gross,¹⁷ in studies of the coronary arteries by means of injection. One notes, therefore, with interest, the significance of the fact that in almost all the cases here reviewed, in which detailed pathologic studies were given, both the anterior and the posterior descending arteries were embarrassed.

The size of the perforation varies from defects admitting only a fine probe to those of about 3 cm. in the longest diameter. The narrower defects are frequently tortuous and difficult to find unless

17. Gross, L.: *The Blood Supply of the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B. Hoeber, Inc., 1921, p. 85.

water or physiologic solution of sodium chloride is poured into the unopened left ventricle. For this reason cases must undoubtedly have been overlooked, the perforation not having been suspected clinically, and therefore not carefully searched for at necropsy.

Thus far all cases reported have been fatal; when calculable, death was found to ensue within ten days after the occurrence of the perforation. But as patients with cardiac infarction without perforation frequently recover, it is to be expected that occasionally in one of those with perforation the infarct may be repaired with scar tissue and the patient may survive. Under such conditions the perforation and, therefore, the physical signs would be expected to persist (unless the former were sealed by a thrombus or by scar tissue).

Cardiac infarction with rupture of a papillary muscle of the left ventricle is the only condition which may lead to confusion in the differential diagnosis. However, in rupture of the papillary muscle the heart is usually markedly widened; the systolic thrills and murmurs are even more bizarre and more pronounced, and a diastolic murmur is more common. The physical signs are either maximal at the apex or equally marked over the entire precordium. Voigt's¹⁸ recent report on rupture of the papillary muscle presents a complete review of this subject.

Congenital patency of the interventricular septum, ruptured congenital aneurysm of the pars membranacea septi, and perforations complicating bacterial endocarditis are easily differentiated by the absence of the syndrome of coronary occlusion and by the comparative youth of most of the patients. In congenital patency, cyanosis, polycythemia, clubbed fingers and the differential facts mentioned at the beginning of this discussion are of additional aid. In bacterial endocarditis the familiar embolic phenomena as well as the result of blood culture will usually confirm the diagnosis.

SUMMARY

1. The literature on perforation of the infarcted septum in coronary thrombosis is reviewed, and an additional case with pathologic findings is reported.

2. The criteria for the diagnosis and differential diagnosis are discussed.

1 East One Hundredth Street.

18. Voigt, W.: Spontanruptur eines Papillarmuskels, zugleich ein Beitrag zur Gestalt des linken hinteren Papillarmuskels, *Ztschr. f. Kreislaufforsch.* **24**:667 (Nov. 1) 1932.

INSULIN AND SUGAR TOLERANCE IN THIN PEOPLE

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BOSTON

Comparatively little is known of the effect of insulin on sugar tolerance in nondiabetic persons. However, certain observations have been reported to suggest that the drug has an appreciable effect on this phase of metabolism. A temporary loss of carbohydrate tolerance during a period of administration of insulin was observed by Wilder, Smith and Sandiford¹ in the case of two obese patients and by Paul, Clark and Gibson² in five normal persons. Schellong and Kramer³ made tests for the sugar tolerance of fourteen thin women before and during insulin therapy and noted a more rapid rise and an earlier fall in the curves for blood sugar during the period of treatment with insulin than during the control period. Fricke⁴ administered dextrose by stomach tube to dogs without inducing glycosuria, but when the same dose of dextrose was combined with injections of insulin, glycosuria of short duration occurred in two and three hours.

Since insulin is now being used widely in the treatment of under-nutrition in nondiabetic persons, it appeared of interest to study more particularly the effect of insulin on the sugar tolerance of such persons. This article, therefore, reports the results of tests for sugar tolerance which were carried out on twenty-five normal thin patients.

PLAN OF INVESTIGATION

The work reported here was carried on according to the following methods: The dextrose tolerance was observed before, during and after the administration of insulin in nine cases, during and after a course of insulin therapy in seven cases and only after insulin had been omitted in nine cases. In the cases studied during a period of treatment

From the Medical Service of the Peter Bent Brigham Hospital.

1. Wilder, R. M.; Smith, F. H., and Sandiford, I.: Observations on Obesity, *Ann. Int. Med.* **6**:724, 1932.

2. Paul, W. D.; Clark, B. B., and Gibson, R. B.: Transient Hyperglycemia and Glycosuria Following Discontinuation of Insulin Given Nondiabetic Patients, *Proc. Soc. Exper. Biol. & Med.* **30**:353, 1932.

3. Schellong, F., and Kramer, H.: Ueber die Ursachen der alimentären Hyperglykämie bei Kohlehydratkarenz (zugleich ein weiterer Beitrag zur Wirkungsweise der Insulin Mastkuren), *Klin. Wchnschr.* **7**:1726, 1928.

4. Fricke, G.: Glykosurie durch Insulin, *Klin. Wchnschr.* **5**:1927, 1926.

with insulin, 10 or 15 units of the drug were taken three times a day for from one to twelve weeks before the test was made, and in the cases studied after insulin was omitted, a period of from three days to two years after the discontinuance of insulin therapy elapsed before the final test was made. A standard dose of 100 Gm. of dextrose was employed. This was mixed with 250 cc. of water, flavored with 50 cc. of lemon juice, chilled and ingested after the patient had fasted for at least fourteen hours. The concentration of sugar in the blood and urine was determined in specimens taken during fasting and at intervals of one-half, one, two and three hours after the ingestion of the dextrose mixture, the determinations of blood sugar being made on 0.1 cc. samples of venous blood according to the micromethod of Folin and Malmros.⁵ The test for sugar in the urine was made with Benedict's solution.

The group studied comprised ten men and fifteen women whose ages varied from 23 to 58 years. Their weights ranged from 85 to 140 pounds (38.55 to 64.5 Kg.) before treatment with insulin, from 91 to 153 pounds (41.27 to 69.4 Kg.) during insulin therapy and from 85 to 180 pounds (38.55 to 81.54 Kg.) after the discontinuance of insulin therapy. Each was more than 15 pounds under standard weight for age, sex and height before the first injection of insulin. None had any demonstrable physical abnormality.

CURVES FOR BLOOD SUGAR

The results obtained can be divided into three groups. In one group, consisting of six persons, the curves for blood sugar were entirely normal throughout the experiment, and the specimens of urine remained persistently sugar-free.

In a second group of six cases, the curves for blood sugar remained essentially normal during the different phases of the study, but during the period of administration of insulin, glycosuria developed. It is interesting to note that in spite of normal levels for blood sugar, there developed in the patients with insulin a concentration of from 0.1 to 1.7 per cent of sugar in the urine, yielding a total excretion of from 0.025 to 0.5 Gm. This appeared one or two hours after the ingestion of dextrose and was transitory.

In the third group, comprising four cases, a considerable increase in the blood sugar developed after the dextrose meal while insulin was being taken. The peak of hyperglycemia occurred one-half or one hour after the ingestion of the sugar and was accompanied by glycosuria in one or two hours. This reached a concentration of from 0.2 to

5. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, *J. Biol. Chem.* **83**:115, 1929.

TABLE 1.—*Sugar Tolerance Showing Normal Curves for Blood Sugar Without Glycosuria**

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy					Length of Time After Discontinuing Insulin Therapy
	Number of Hours After Ingestion of Dextrose					Number of Hours After Ingestion of Dextrose					Number of Hours After Ingestion of Dextrose					
	Fast-ing	½	1	2	3	Fast-ing	½	1	2	3	Fast-ing	½	1	2	3	
1.	125	151	148	133	80	112	140	146	122	80	111	156	...	99	85	
2.	92	98	105	102	72	117	140	103	95	94	97	128	97	82	74	
3.	103	175	166	133	109	89	100	132	133	80	97	118	99	87	80	
4.	88	119	125	88	85	76	121	104	98	68	
5.	87	144	156	124	70	90	154	154	114	83	
6.	133	144	151	144	104	99	148	148	138	101	

* In tables 1 to 4, values are expressed in milligrams per hundred cubic centimeters.

TABLE 2.—*Sugar Tolerance Tests Showing Normal Curves for Blood Sugar with Glycosuria During Treatment with Insulin*

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy					Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy					Length of Time After Discontinuing Insulin Therapy
	Number of Hours After Ingestion of Dextrose					Number of Hours After Ingestion of Dextrose					Number of Hours After Ingestion of Dextrose					
	Fast-ing	½	1	2	3	Fast-ing	½	1	2	3	Fast-ing	½	1	2	3	
7...	96	119	144	88	77	100	146	154*	114*	96	89	149	160	97	85	
8...	100	148	125	113	100	85	126	147*	97	95	83	160	102	74	72	
9...	93	148	149	125	105	104	167	141*	92*	91	105	166	138	125	102	
10...	75	100	111	85	73	108	137	125*	106	80	105	133	133	87	80	
11...	100	100	125	95	84	103	130	141*	143	108	98	103	124	111	100	
12...	98	132*	156	100	66	97	117	130	80	86	

* From 0.025 to 0.5 Gm. of sugar was excreted in the urine.

TABLE 3.—*Tests for Sugar Tolerance Showing Hyperglycemia and Glycosuria with Insulin Therapy*

Patient	Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose Before Administration of Insulin				Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose During Period of Insulin Therapy				Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy				Length of Time After Discontinuing Insulin Therapy		
	Number of Hours After Ingestion of Dextrose				Number of Hours After Ingestion of Dextrose				Number of Hours After Ingestion of Dextrose						
	Fast-ing	½	1	2	3	Fast-ing	½	1	2	3	Fast-ing	½		1	2
13.....	79	116	85	80	74	114	154	185*	104*	102	109	109	116	102	2 weeks
14.....	104	196	200*	103*	80	102	141	126	108	10 weeks
15.....	100	170*	171*	111*	97	84	103	134	103	1 day
16.....	107	158	196*	103*	100	125	180	200	149†	6 days
16.....	105	145	150	128	3 months

* From 0.08 to 0.4 Gm. of sugar was excreted in the urine.

† The slightest possible trace of sugar was present in the urine.

1.8 per cent of sugar in the urine, yielding a total excretion of from 0.08 to 0.4 Gm. of sugar. The curve for blood sugar in these instances was of the type usually encountered in mild diabetes and suggested, definitely, a transitory depression of sugar tolerance.

In order to ascertain whether the sugar tolerance was in any way permanently impaired by insulin, tests for sugar tolerance were carried out on a group of nine patients who had received the drug over a long period of time. The final test for sugar tolerance was made from four months to two years after administration of the drug had stopped. For all of these patients the curves for blood sugar were normal, and there was no glycosuria.

Finally, since a decreased tolerance to 100 Gm. of dextrose occurred in some of the patients while they were taking insulin, it appeared of

TABLE 4.—*Sugar Tolerance After the Omission of Insulin**

Blood Sugar Levels in Patients Receiving 100 Gm. of Dextrose After Discontinuing Insulin Therapy						Length of Time After Discontinuing Insulin Therapy
Patient	Fasting	Number of Hours After Ingestion of Dextrose				
		½	1	2	3	
17.....	89	136	121	109	80	16 months
18.....	80	156	166	122	80	11 months
19.....	94	118	110	109	80	17 months
20.....	96	...	111	91	...	13 months
21.....	98	133	111	87	84	2 years
22.....	101	128	...	129	118	14 months
23.....	80	110	178	101	98	2 months
24.....	105	...	133	105	100	2 years
25.....	101	120	72	96	81	4 months

* No tests for sugar tolerance were made on these patients before or during treatment with insulin.

practical value to test the urine and the blood for sugar while the patients were taking their usual diets during various periods of observation. With this in mind, occasional samples of urine or of blood were collected after various meals and examined for sugar. In no instance was there any glycosuria or hyperglycemia either during or after the period of insulin therapy.

COMMENT

At present the cause of the results obtained in this study is largely a matter of speculation. The appearance of glycosuria without hyperglycemia suggests that insulin may have an effect on the kidney, causing a decreased renal threshold to sugar or an increased permeability to it. Such an effect, however, may appear improbable in the light of evidence obtained by other workers. Rabinowitch⁶ showed that in certain diabetic persons the renal threshold rises substantially after the use of

6. Rabinowitch, I. M.: Observations on the Altered Renal Threshold for Sugar in Insulin—Treated Diabetics, *Brit. J. Exper. Path.* 7:352, 1926.

insulin, and van Creveld and van Dam's⁷ experiments on surviving frogs' kidneys indicate that insulin tends to decrease rather than to increase the permeability of the glomerular membrane to sugar.

The appearance of a transient glycosuria after the administration of insulin and sugar with an elevation of the level for blood sugar suggests that insulin may cause an increase in the rate of absorption of sugar from the gastro-intestinal tract or possibly a temporary but perceptible decrease in the pancreatic function.

That insulin increases absorption of food has already been proposed by Blotner⁸ and by Koref and Mautner.⁹ Cori and Cori,¹⁰ too, have shown by experiments on rats that insulin increases the rate of absorption of dextrose from the intestinal tract.

There is evidence to suggest that insulin may cause a temporary decrease in pancreatic function. McJunkin and Roberts¹¹ found that injections of insulin inhibited the mitotic activity of the pancreatic islet cells in young rats. Wilder, Smith and Sandiford¹ and Paul, Clark and Gibson² explained the phenomenon of glycosuria and hyperglycemia following administration of insulin as due to a diminished irritability of the rested pancreas or to inhibition of the normal islet secretion in compensation for the excessive amount of insulin present following its injection.

Such a suppression of pancreatic function might be analogous to the reaction of certain endocrine glands, such as the ovaries and the parathyroid glands, when the endocrine products derived from those glands are administered. For example, Graber and Cowles¹² have inhibited normal ovarian activity with corpus luteum extracts and Goldman and Aub¹³ have depressed normal parathyroid function with parathyroid extract-Collip.

Regardless of the cause of the decreased sugar tolerance induced by insulin in some cases, it is of value to know that this finding is of

7. van Creveld, S., and van Dam, E.: *De invloed van alcoholische pancreas-extracten (Insule) op het gedrag der nieren tegenover glucose*, *Nederl. tijdschr. v. geneesk.* **2**:1498, 1923.

8. Blotner, H.: *Observations on the Effect of Insulin in Thin Persons*, *J. A. M. A.* **100**:88 (Jan. 14) 1933.

9. Koref, O., and Mautner, H.: *Zur Resorptionbeschleunigung durch Insulin*, *Klin. Wchnschr.* **5**:191, 1926.

10. Cori, C. F., and Cori, G. I.: *The Fate of Sugar in the Animal Body*, *J. Biol. Chem.* **76**:763, 1928.

11. McJunkin, F. A., and Roberts, B. D.: *Effect of Excessive Insulin on the Pancreatic Islets of Young Rats*, *Proc. Soc. Exper. Biol. & Med.* **29**:893, 1932.

12. Graber, H. T., and Cowles, R. A.: *Effect of Corpus Luteum Extracts in Suppressing Ovarian Activity in Rats*, *Proc. Soc. Exper. Biol. & Med.* **28**:977, 1931.

13. Goldman, D., and Aub, J. C.: *Personal communication to the author.*

no practical importance. The sugar tolerance returns to normal in a short while. In patients of the series studied it has remained normal two years after the omission of insulin, and there has not been noted sufficient depression of pancreatic function to cause any disturbance in the carbohydrate metabolism when the patients were taking their usual diets.

SUMMARY

This contribution presents a study on the effect of insulin on sugar tolerance in twenty-five thin persons who gained weight by the use of this drug. Tests were made before treatment in nine cases, after one to twelve weeks of continuous administration of insulin in sixteen cases and, finally, from three days to two years after the cessation of administration of insulin in all cases.

Three types of curves for sugar tolerance were obtained. In one, the curves for blood sugar were normal, and the urine remained sugar-free during all the periods of observation. In the second, the curves for blood sugar were normal during the various periods of study, but during the period of administration of insulin glycosuria appeared, usually one or two hours after the ingestion of the dextrose. In the third type, the curves for blood sugar were normal either before or after the use of insulin, but during the period of treatment with insulin there developed a considerable increase in the concentration of the blood sugar in one-half or one hour after the ingestion of dextrose; this was associated with glycosuria, which usually appeared in one or two hours.

The cause of the temporary decrease in tolerance induced by insulin is a matter of speculation. It is suggested that the type of tolerance associated with glycosuria and normal curves for blood sugar is due to a decreased renal threshold and the type associated with glycosuria and hyperglycemia, to either an increased absorption of sugar from the gastro-intestinal tract or a temporary suppression of pancreatic function.

Regardless of the cause of the glycosuria and hyperglycemia encountered, the finding was of no practical significance, since the sugar tolerance invariably returned to normal shortly after insulin was omitted. Decrease in tolerance to the customary diets employed by these patients while they were taking insulin for the purpose of gaining weight was not observed, even though the diets contained abundant amounts of carbohydrate.

Book Reviews

Tuberculin: Its Vindication by Technique. With Special Reference to Tuberculous Disease of the Eye. By W. Camac Wilkinson, M.D. (London), F.R.C.P., Hon. Director, Tuberculin Clinic, London. Price, 10 shillings, 6 pence. Pp. 93, with 31 illustrations. London: J. & A. Churchill, 1933.

Sixty-eight of the ninety-three pages of this monograph are devoted to a report on the diagnosis and treatment of ocular tuberculosis by tuberculin, and the balance to an impassioned plea for its use in pulmonary tuberculosis. "Nothing can take the place of tuberculin in the early diagnosis of phthisis. It can definitely exclude phthisis as nothing else can, which is a transcendent advantage, but it can also, with other methods, definitely discover that tubercle bacilli are working mischief in the tissues long before any other method can do so. Moreover, as the transcendental remedy for the treatment of early phthisis, it leaves little to be desired. . . ." The author refers to previous reports of his which purport to prove his contention and states that he has a mass of additional evidence but does not present any of it. He pleads for the establishment of about two hundred "Tuberculin Clinics" in London alone, and contends that ambulatory treatment with tuberculin will save taxpayers large sums, and that only patients with the severer types of consumption should be sent to sanatoria. He complains that tuberculin has never been given a fair trial by others, but has been proved by him to be a most potent agent.

The data concerning tuberculin in the diagnosis and treatment of ocular tuberculosis consist of a report on its use in forty-three patients sent to the clinic by oculists in the last five years. In an evaluation of these data one may first question the inclusion of a case of Parinaud's disease and one of "advanced myopia with chorio-retinitis and atrophy," and then comment that in not a single case can the reader venture more than a guess as to what the real condition of the eye was. One is asked to accept the diagnosis without question. For diagnosis the author makes combined intracutaneous and subcutaneous use of the tuberculin (TR.) but does not give details, rules or even the basis for his conclusion that any given case is or is not one of tuberculous disease of the eye except that a temperature and the "track" (local?) reaction were present. Details of treatment, dosage, intervals, what to watch for and other facts are likewise inexcusably meager. In the face of this the author insists that the treatment is often incorrectly given by others. He stresses the value of long-continued treatment—"not for months but for years, even many years."

In one respect, however, the contribution is greatly to be praised, in contrast with various otherwise notable and valuable continental monographs on the use of tuberculin in work on the eye; namely, the author does state in each case the length of time the condition of the eye remained quiescent or "cured" after treatment was completed. Of the forty-three cases, the reviewer would first eliminate eight (the diagnosis was in doubt in three; treatment was still going on in three; in one the patient was still active, and in one the patient had stopped treatment). The thirty-five remaining cases include twenty-six of iridocyclitis (acute and chronic), one of nodular iritis, two of vitreous hemorrhage, two of retinal disease, one of interstitial keratitis and others.

The period of observed quiescence varied from two to forty-five months (with only three observed over three years); it was less than one year in three cases (average, four and one-half months), and in the entire thirty-five cases averaged only sixteen and one-half months.

The reviewer considers this period of observation definitely inadequate. In a follow-up report of fifty cases of iritis, Brown and Irons (*The Etiology of Iritis*, J. A.

M. A. 81:1770 [Nov. 24] 1923) set up a period of three years as the shortest period of freedom from recurrence after which one may at all fairly speak of a "cure."

As stated, this record of freedom from occurrence constitutes a very praiseworthy feature of the monograph, inadequate as it is, but there is little else in the work which will stand fair criticism.

L'exploration fonctionnelle de la rate. By E. Benhamou. Price, 50 francs. Pp. 255, with 103 illustrations. Paris: Masson & Cie, 1933.

This book is interesting and to be highly recommended. When one considers that but a few years ago not much was known about the spleen, it is refreshing to discover how great has been the knowledge lately developed regarding the diagnosis and treatment of the various splenic disorders.

Benhamou has attempted to apply to the clinical study of splenic function the physiologic approach to the subject introduced by Barcroft in England, Binet and Pagniez in France and Scheunert in Germany. He then develops his thesis, describing the methods which he employs. He mentions what facts relating to the spleen are to be gleaned by customary physical examination and shows excellent photographic reproductions and charts to demonstrate that most accurate pictures of the organ can be obtained by x-ray either with or without the aid of thorotrast. Of even greater value in determining splenic function, however, is the spleen's response to the subcutaneous administration of epinephrine manifested in the red blood cell count, the white blood cell count, the platelet count, the reticulocytic count and in the character of the circulating leukocytes.

Benhamou believes that spleens which are enlarged from different causes yield varied responses to epinephrine, and that such varied responses afford a means of classifying the underlying pathologic process and suggesting appropriate treatment. In certain instances, for example, splenectomy is indicated, whereas in others this operation is likely to prove fatal so that other forms of treatment are preferable. Study of splenic function helps to separate these two groups.

The book is well printed and bound in paper. A comprehensive bibliography of 303 references completes it. On the whole, the volume deserves favorable comment and should help to stimulate further investigation.

Modern Aspects of Gastro-Enterology. By M. A. Arafa. Price, \$8.25. Pp. 374. New York: William Wood & Company, 1933.

In no branch of medical literature is the atavistic tendency more dominant than in textbooks of gastro-enterology. The same exposition of a sharply crystallized body of doctrine appears over and over again, modified, perhaps, by the teachings of some physiologist who for the moment is approved by the gastro-enterologic group. There seems to be a curious imperviousness of these books to outside influences; one suspects that there even exists a proscribed list of writings which challenge traditional concepts. It is with interest, therefore, that one approaches Arafa's recent book; one hopes that under the title of "Newer Aspects of Gastro-Enterology" one may find that the house has been cleaned and the cobwebs swept away. Dr. Arafa's work shows all the earmarks of a sincere effort; clearly he has labored industriously in producing this compilation. But the same old outline is followed, and for the most part there is presented only traditional material strongly tintured by the teachings of the Hurst school.

No two men will agree in all details, and the reviewer finds on nearly every page points with which he would take issue. The statement that "achylia responds to histamine stimulation" in sprue but not in pernicious anemia (p. 68) has not held true in his experience. On page 77 it is said that "evidence is accumulating" that the achlorhydria of later life is due to gastritis; what this evidence is the reviewer does not know. The exposition of the etiology of gastritis—that elusive entity—

goes on with moral fervor if not with medical soundness when one is told that whisky, brandy, liquors and gin are particularly important factors and that gastritis "is not uncommon among young people who frequent cocktail parties." When the author proceeds to say, without any evidence, that "excessive smoking is a common cause (of gastritis), and that tea and coffee may have a similar though more mild, detrimental effects" one's amusement begins to give place to annoyance (p. 77). Nor can the reviewer agree (p. 103) that gastric lavage is a cure for chronic gastritis, or that toxins absorbed from remote "foci of infection" are excreted by the gastric and duodenal mucous membrane, thereby producing peptic ulcer (p. 113). One could continue indefinitely.

The book is well written, well illustrated and in every sense useful, and while not the reviewer's ideal of what can be done in this domain, it has fewer positive demerits than other textbooks of gastro-enterology with which he is familiar.

History of Urology. Prepared under the auspices of the American Urological Association. Editorial Committee, Edgar G. Ballenger, William A. Frontz, Homer G. Hamer and Bransford Lewis, Chairman. Two volumes. Price, \$8. Pp. 746, with illustrations. Baltimore: Williams & Wilkins Company, 1933.

These two volumes combine to make an interesting book. It was written by thirty-two well known contributors, and deals primarily with the history of urology in this country. As Dr. Wishard suggests in the preface, the specialty is a youthful one. It began in 1874 with the publication of Van Buren and Keyes's "Genito-Urinary and Venereal Diseases," soon gathered momentum and has made amazing strides since 1900. Any one who enjoys reading about medical personalities will like the first eight chapters of this history. These give short accounts of the pioneer urologists in various parts of the country, showing how urology came to be recognized as a specialty through the work of various leaders of medical and surgical thought all over the United States.

The remainder of volume 1 and all of volume 2 deal more directly with the development of present knowledge regarding various phases of the specialty. Anatomy, physiology and bacteriology, as well as improving technics, instruments, diagnostic measures, roentgenology and methods of anesthesia and therapy, are discussed. Each of these chapters is written in an orthodox textbook style and has references appended so that all the pertinent literature is made easily available.

The editorial board has worked carefully. There is a certain amount of unevenness in the manner in which various chapters have been written, and occasionally names are spelled incorrectly. Considering the number of contributors, however, and the size of the two volumes, there is little to be criticized. The printing is good, and the illustrations are sufficiently clear and interesting. On the whole, this "History of Urology" lends dignity and completeness to any medical library.

Peptic Ulcer. By Jacob Buckstein. Second edition. Price, \$12. Pp. 417, with 334 roentgenograms and 77 illustrations. New York: Paul B. Hoeber, Inc., 1933.

The second edition of this monographic atlas has been considerably enlarged by the addition of 121 illustrations and the incorporation of the latest literature on the subject. The result is a splendid book replete with illustrations which will be of great value to the roentgenologist who has a relatively slight opportunity of observing many cases of peptic ulcer. This book and the other monographs in the series have been prepared in order to supply a series of master roentgenograms for study and for comparison. Just how the atlas would fit into the library of the internist is a rather difficult question to answer. Of course, it would be of considerable value to the roentgenologist who makes roentgen diagnoses at relatively frequent intervals, but whether or not the high initial cost of the book would repay the rather infrequent reference to it by the practitioner when questionable films of the upper alimentary tract come up for interpretation

would be a difficult matter to judge. It would seem that the atlas would be employed almost entirely by the roentgenologist and would be of decidedly limited value to the internist.

The atlas is beautifully illustrated. The format is what one has come to expect of Hoeber's books.

La angina de pecho. By Dr. Gregorio N. Martinez. Pp. 278. Buenos Aires: Humberto Andreetta, 1933.

This is an excellent monograph on angina pectoris based on the author's experience and on an extensive review of the literature. The bibliography contains 652 titles. The book is well illustrated not only with electrocardiograms, but with attractive colored illustrations. Particularly interesting are the ones showing diagrammatically the various operations that have been performed with the hope of relieving the pain of angina. The author inclines to the view that the ideas of Danielopolu are the nearest correct. He realizes that many of the attempts at operative relief have failed, but he believes that enough of them have been successful to warrant further attempts along this line.

As one would expect, there is not much new in regard to either pathology or treatment, but to any student of the subject able to read Spanish this book can serve as a splendid introduction to the subject of angina. The author is particularly to be congratulated on having been able to cover the literature so well while working in a country far removed from the larger medical libraries.

Arteriosclerosis. Edited by Dr. E. J. Cowdry. Price, \$5. Pp. 617, with 88 illustrations. New York: The Macmillan Company, 1933.

This volume is a publication of the Josiah Macy, Jr., Foundation and aspires to bring together current knowledge and opinion regarding the changes in the blood vessels generally termed arteriosclerosis. It is a compilation of ideas from various sources: The authors are drawn from Europe and England, as well as from different sections of this country.

The subject matter is well arranged, beginning with a historical review by Dr. Esmond R. Long of Philadelphia of how present knowledge regarding arteriosclerosis has developed, and ending with a critical review of the contents of the book by Dr. Alfred E. Cohn of New York. Throughout, one finds chapters on the different phases of vascular disease written from various points of view by thoroughly competent authorities.

On the whole, the book is excellent for reference. It is well printed and illustrated; each chapter is clearly written, and the literature is covered adequately. All medical libraries will wish to own a copy.

Le sinus carotidien et la zone homologue cardio-aortique. By C. Heymans, J. J. Bouckaert and P. Regniers. Price, 55 francs. Pp. 334. Paris: Gaston Doin & Cie, 1933.

The name of Heymans has been prominently associated with work on the problems of the carotid sinus, and the present volume of which Heymans the younger is chief author is dedicated to his father. While (and properly) a great deal of emphasis is placed on the work of the Belgian group, the subject is treated in systematic form, and the literature in general is well covered. Each topic, such as the relation of the carotid sinus to respiration or to blood pressure, receives detailed and critical consideration. The experimental support for any claims is well presented, and clinical implications are exposed.

The physiologist working in this special domain will doubtless take issue with certain points, but in any event the monograph represents a monumental collection of material. The style is elegant, the format pleasing, and to the worker who wishes quickly to inform himself on the status of the subject the work should prove invaluable.

Food and the Principles of Dietetics. By Robert Hutchinson and V. H. Mottram. Seventh edition. Price, \$7.25. Pp. 630. New York: William Wood & Company, 1933.

Many books are available on practical dietetics as well as on the composition of foods. Few, however, combine a thorough discussion of feeding from both of these angles. In the present instance a happy combination has been achieved, the result of which should be of great help to the practicing physician; that such is actually the case is witnessed by the fact that this is the seventh edition of Hutchinson and Mottram's treatise, the first having appeared in 1900. The reviewer is especially impressed by the scholarly fashion in which the nature of foods, their individual composition, their digestibility and their fate in the body are discussed; with bread, for example, one is told about wheat, the milling process and the making of flour, and is enlightened as to the baking of bread, the composition of the final loaf, its nutritive value and even its economic status. The sections on diet in special diseases are terse but adequate. The bibliography is well selected, and the index is complete.

Fortschritte der Serologie. By Hans Schmidt, M.D., Professor of Hygiene, Institute for Experimental Therapy, Marburg. Paper. Price, 12 marks. Pp. 196, with 20 figures. Dresden: Theodor Steinkopff, 1933.

This book is the thirtieth part of a series of short German monographs which have been appearing from time to time since 1921, designed to summarize the progress of investigation in different paths of science. This particular publication deals, as its title suggests, with recent progress in serologic tests.

The book is well printed and clearly written. The subject matter covers such topics as the formation of antigen; the phenomena of agglutination, precipitation and hemolysis; complement fixation; phagocytosis; bacteriolysis; the formation of toxin and antitoxin, and lipoids in serologic reactions. The bibliography is adequate, with abundant references to constructive work which has been completed in various American, English, French and German laboratories. A complete table of contents is appended. On the whole, the book is useful for reference, and will make an acceptable addition to many medical libraries.

Les fonctions gastro-duodénales. By J. Dimitresco-Popovici. Paper. Price, 28 francs. Pp. 250. Paris: Masson & Cie, 1932.

This book gives a rapid and necessarily incomplete summary of physiologic and clinical researches on the stomach and duodenum, including some of the author's own work. The book should prove to be stimulating to the American reader, who will find no mention of much that has excited attention in this country, but instead will find occasional things which have escaped his notice in the European literature. One must regret the unusual number of inaccuracies and omissions in the bibliography and the absence of an index.

The Therapeutic Agents of the Quinoline Group. By W. F. von Oettingen, M.D., Ph.D. American Chemical Society Monographs. Price, \$6. New York: The Chemical Catalog Company, Inc., 1933.

This book is really a small encyclopedia on the subject. About 500 derivatives of the quinoline group are discussed from every possible angle: chemical, pharmacologic, physiologic, toxicologic and therapeutic. Little more can be said in review; the monograph seems to cover the subject to date in a definitive manner. The bibliography includes about 1,000 titles.

La función hemo-respiratoria en los "Cardiacos Negro de Ayerza." By Isaac Berconsky. Buenos Aires: Biblioteca de la Facultad de Ciencias Medicas, 1933.

This rather brief monograph on Ayerza's disease represents almost entirely a more or less philosophic discussion of the various explanations that have been brought forth to explain the cyanosis that occurs in the disease. It is an excellent review of the literature, without presenting any new experimental evidence as to the mechanism of the production of the disease.

News and Notes

GERMAN SOCIETY FOR CIRCULATORY RESEARCH

The seventh convention of the German Society for Circulatory Research (Deutsche Gesellschaft für Kreislaufforschung) will be held at Bad Kissingen on April 16 and 17, 1934. The subjects to be discussed are thrombosis and embolism.

Applications for participation will be accepted until March 1 by Prof. E. Koch, Bad Nauheim.

A detailed program will be mailed to those who register.

PROF. DR. J. NÖRR, *Chairman*,
München, Veterinärstr. 6

THE HEART IN MYXEDEMA

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AND

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BOSTON

A review of the literature on the subject of the heart in myxedema reveals a certain amount of confusion concerning the true nature of the cardiac findings. There are those who feel that the findings are purely incidental; others believe that they are inherent in the disease. This lack of unanimity of opinion is found not only in clinical observations but also in experimental, physiologic and pathologic studies. In our attempt to throw light on this problem, it is our purpose to present a critical review of the literature and to report further clinical observations.

REVIEW OF THE LITERATURE

The first extensive study on the heart in myxedema was made by Zondek.¹ His original contribution was based on four cases; later he mentioned additional cases. He found diffuse cardiac enlargement, occasionally limited to the left side, and by fluoroscopy he noted sluggish muscular contractions of the enlarged heart. In the electrocardiographic tracing he observed flat P waves, flat or inverted T waves and low R waves. These changes were interpreted as a result of the diminution in the strength of contractions of the auricle and ventricle inherent in myxedema. Clinically, the symptoms of decompensation were always mild, edema and congestive failure occurring but seldom. The blood pressures were normal. Under thyroid therapy, the condition returned to normal. He suggested using the electrocardiographic findings as an index to the dosage of thyroid to be administered.

From the Thyroid Clinic, the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Zondek, H.: *Das Myxödemherz*, München. med. Wchnschr. **65**:1180, 1918; **66**:681, 1919; *Stoffwechsel und Herzbefunde bei den Kramerschen Myxödemen*, Berl. klin. Wchnschr. **55**:989, 1918; *Behandlung der Herzdilatationen bei Schilddrüseninsuffizienz*, Therap. d. Gegenw. **60**:361, 1919; *Herz und innere Sekretion*, Ztschr. f. klin. Med. **90**:171, 1920; *Herzbefunde bei endokrinen Erkrankungen*, Deutsche med. Wchnschr. **46**:1239, 1920.

Many authors have confirmed Zondek's findings,² and Cori³ reported similar observations in a 4 year old cretin. The eleventh edition of Osler's "Principles and Practice of Medicine"⁴ states that in myxedema, "myocardial insufficiency of various grades is not uncommon and may disappear after thyroid treatment is given." Sturgis⁵ noted definite cardiac injury in 40 per cent of his cases, and in Lawrence's⁶ series, every case of demonstrable myxedema showed signs of cardiovascular disease. Other writers have made additional observations. Gardner⁷ noted periods of auricular flutter, arborization block and inverted T waves in the electrocardiogram, which disappeared under thyroid therapy. Lueg⁸ questioned whether changes in the electrocardiogram might not be due to changes in the current in passing through the tissues between the heart and the galvanometer, and Tung⁹ suggested anoxemia or a myxedematous state of the cardiac muscle as a cause of the changes in the tracing. Holzman¹⁰ felt that possibly the long duration of the myxedema might produce definite organic changes in the heart in some cases. Somewhat similarly, White¹¹ expressed a belief that coronary disease accounts for the greater frequency of cardiac damage among

2. (a) Fahr, George: Myxedema Heart, *J. A. M. A.* **84**:345 (Jan. 31), 1925; (b) Myxedema Heart, *Am. Heart J.* **3**:14, 1927. (c) Schittenhelm, A., and Eisler, B.: Ueber die Wirksamkeit des Thyroxins bei endokrin bedingten Störungen, *Klin. Wchnschr.* **6**:1935, 1927. (d) Amargos, A.: Clinical Aspects of Myxedematous Cardiac Insufficiency, *An. Fac. de med., Montevideo* **13**:339, 1928. (e) Blumer, George, in *Bedside Diagnosis*, by American authors, Philadelphia, W. B. Saunders Company, 1928, vol 3. (f) Duden, C.: Myxedema with Cardiac Decomensation and Hypertension Which Disappeared with Thyroid Medication, *J. Missouri M. A.* **26**:25, 1929. (g) Davis, J. C.: Myxedema Heart with Report of One Case, *Ann. Int. Med.* **4**:7, 1931. (h) Norris, G. W., and Landis, H. R. M.: *Diseases of the Chest*, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

3. Cori, G.: Experimentelle Untersuchungen an einem kongenitalen Myxödem, *Ztschr. f. d. ges. exper. Med.* **25**:150, 1921.

4. Osler, William: *Principles and Practice of Medicine*, ed. 11, New York, D. Appleton and Company, 1930.

5. Sturgis, C. C.: The Cardiovascular System in Diseases of the Thyroid Gland, *J. Michigan M. Soc.* **26**:1, 1927.

6. Lawrence, C. H.: The Physiological Background for the Symptoms of Thyroid Failure, *Boston M. & S. J.* **196**:2, 1927.

7. Gardner, E. L.: Hypothyroidism with Special Reference to the Minor Deficiencies, *Journal-Lancet* **44**:10, 1924.

8. Lueg, W.: Ueber das Elektrokardiogramm des Myxödems, *Ztschr. f. klin. Med.* **104**:337, 1926.

9. Tung, C. L.: The Status of the Heart in Myxedema, *Am. Heart J.* **6**:734, 1931.

10. Holzman, J. E.: Myxedema Heart, *Am. Heart J.* **4**:351, 1929.

11. White, P. D.: *Heart Disease*, New York, The Macmillan Company, 1931.

the older cases of myxedema. Ayman, Rosenblum and Falcon-Lesses¹² suggested that enlargement of the heart, with its return to normal following thyroid treatment, is the one diagnostic feature of the heart in myxedema, since the other abnormalities are usually found in all cases of myxedema.

Several writers have limited their reports to electrocardiographic findings. A number of them¹³ have corroborated Zondek's original findings. Others¹⁴ reported similar observations both in cretins and in patients with myxedema. In two cases Chini¹⁵ found the typical coronary T wave described by Pardee.¹⁶ Hamburger, Lev, Priest and Howard¹⁷ found that the electrocardiographic changes may precede the change in the basal metabolic rate. Lesser and Anderson¹⁸ described a patient, aged 51, with myxedema who had attacks of paroxysmal tachycardia of seventeen years' duration. Two electrocardiograms taken before treatment was instituted showed, in the first instance, paroxysmal nodal tachycardia, with a pulse rate of 168 and depressed S T intervals, and, in the second instance, a sinus bradycardia with a rate of 40, inversion of the T waves in all leads and a low take-off of S T, with upward convexity in lead II. Six months after treatment the electrocardiogram showed normal sinus rhythm, a rate of 79, T upright in all leads and a normal S T interval.

12. Ayman, D.; Rosenblum, H., and Falcon-Lesses, M.: Myxedema Heart Without Evidence of Cardiac Insufficiency: Report of Two Cases, *J. A. M. A.* **98**: 1721 (May 14) 1932.

13. (a) Means, J. H., and Richardson, E. P.: Diseases of the Thyroid, in Christian, H. A.: *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1929, vol. 4. (b) Willius, F. A., and Haines, S. F.: Status of the Heart in Myxedema, *Am. Heart J.* **1**:67, 1925. (c) Reid, W. D., and Kenway, F. V.: Electrocardiographic Signs Associated with Low Basal Metabolism, *Endocrinology* **13**:191, 1929. (d) White, P. D., and Aub, J. C.: The Electrocardiogram in Thyroid Disease, *Arch. Int. Med.* **22**:766 (Dec.) 1918.

14. Thacher, C.: The Electrocardiogram in Cretinism and Mongolian Idiocy, *Am. J. Dis. Child.* **28**:25 (July) 1924. Nobel, E.; Rosenblüth, A., and Samet, B.: Das Elektrokardiogramm des kindlichen Myxödems, *Ztschr. f. d. ges. exper. Med.* **43**:332, 1924. Thacher, C., and White, P.: The Electrocardiogram in Myxedema, *Am. J. M. Sc.* **171**:61, 1926.

15. Chini, V.: Breve nota di cardiologia sul mixedema, *Cuore e circolaz.* **13**: 32, 1929.

16. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, *Am. J. M. Sc.* **169**:270, 1925.

17. Hamburger, W. W.; Lev, M. W., Priest, W. S., and Howard, H. C.: The Heart in Thyroid Disease, *Arch. Int. Med.* **43**:1 (Jan.) 1929.

18. Lesser, H., and Anderson, E. M.: Three Cases of Adult Myxedema in Women, *Endocrinology* **15**:5, 1931.

Others have paid attention only to changes in the size of the heart. Several authors¹⁹ reported findings similar to those of Zondek. Christian²⁰ in his early cases did not note these changes, but later²¹ mentioned that in a few patients with myxedema who showed enlargement of the heart and symptoms of congestive failure, digitalis medication was without effect, while thyroid therapy resulted in marked improvement. Wegelin²² expressed the opinion that enlargement of the heart is due less to changes in the myocardium than to a decrease in the number of red blood cells and to bradycardia. Eppinger²³ described many cases resembling myxedema in their appearance (no basal metabolic rates are recorded), with enlargement of the heart and symptoms of heart failure, that showed a complete return to normal following thyroid treatment.

In contrast to the workers mentioned, there are those who feel that changes in the heart in myxedema are of no great importance or significance. Cabot,²⁴ Cecil,²⁵ Vaquez²⁶ and MacKenzie²⁷ made no mention of the status of the heart in myxedema. Hirschfelder²⁸ stated that cardiac symptoms of cachexia thyreopriva are not prominent features of the disease. Means and Richardson^{13a} noted that the lack of tone to the extent of gross cardiac enlargement occurs but rarely, and Means, White and Krantz²⁹ stated that about all that can be said is that occa-

19. Assmann, H.: *Das Myxödemherz*, München. med. Wchnschr. **66**:9, 1919. Meissner, R.: *Zur Klinik des Myxödemherzens*, München. med. Wchnschr. **67**:1316, 1920. Zandrén, S.: *Zur Frage des Myxödemherzens*, Zentralbl. f. Herz. u. Gefässkr. **14**:183, 1922. Zins, B., and Rösler, H.: *Kasuistischer Beitrag zur Beeinflussung des Myxödemherzens durch Thyreodin*, Wien. klin. Wchnschr. **39**:1360, 1926.

20. Christian, H. A.: *The Heart and Its Management in Myxedema*, Rhode Island M. J. **8**:109, 1925.

21. Christian, H. A.: *Myocardial Disturbances Due to Abnormal Thyroid Function and Their Management*, Pennsylvania M. J. **32**:70, 1928.

22. Wegelin, C.: *Drüsen mit innerer Sekretion*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8, p. 353.

23. Eppinger, H.: *Zur Pathologie und Therapie des menschlichen Ödems*, Berlin, Julius Springer, 1917.

24. Cabot, Richard C.: *Physical Diagnosis*, ed. 10, New York, William Wood & Company, 1930.

25. Cecil, R. L.: *Text Book of Medicine*, ed. 3, Philadelphia, W. B. Saunders Company, 1930.

26. Vaquez, H.: *Diseases of the Heart*, Philadelphia, W. B. Saunders Company, 1924.

27. MacKenzie, J.: *Diseases of the Heart*, ed. 5, New York, Oxford University Press, 1925.

28. Hirschfelder: *Diseases of the Heart and Aorta*, ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 675.

29. Means, J. H.; White, P. D., and Krantz, C. I.: *Observations on the Heart in Myxedema*, Boston M. & S. J. **195**:10, 1926.

sionally a patient with myxedema presents a type of cardiac flabbiness which in reality is due to the low level of the metabolic ratio. In a series of fifty-eight cases, Case³⁰ did not associate the few cardiac findings with myxedema. Curschmann³¹ noted the changes in the size of the heart, but he found no variation in the electrocardiogram, while Doxiades and Pototzky³² observed electrocardiographic changes without cardiac enlargement. Coelho³³ does not consider the electrocardiographic findings typical of myxedema, as he has seen similar tracings in other diseases, notably, in Addison's disease and in Fröhlich's syndrome. He does not believe that cutaneous resistance plays any part in the picture, since in these cases the use of needle electrodes gave the same results as the use of ordinary electrodes.

In addition to the work on the size of the heart and electrocardiographic changes in myxedema, numerous isolated observations on other changes of the cardiovascular system associated with thyroid deficiency have been reported. Most important among these observations have been those on heart block, angina pectoris, edema and hypertension.

Incomplete heart block was present in a case reported by Luten.³⁴ The patient improved under thyroid therapy, while in a case of complete heart block reported by Aub and Stern³⁵ thyroid therapy had no appreciable effect. A few observations have been made on the effect of thyroid therapy on complete heart block in which evidence of myxedema was lacking. Blackford and Willius³⁶ expressed the belief that thyroid medication quickens the idioventricular rate, the auricular rate increasing much earlier than the ventricular. In a case reported by Drake³⁷ the final picture was that of normal rhythm and intraventricular

30. Case, C. E.: An Analysis of Fifty-Eight Cases of Myxedema, Clifton M. Bull. **11**:112, 1925.

31. Curschmann, H.: Ueber Myxödem der Erwachsenen, Med. Klin. **22**:559, 1926.

32. Doxiades, L., and Pototzky, C.: Die Bedeutung der kardiovaskulären Untersuchungsmethoden für die Beurteilung des Mönkolismus und des Myxödems beim Kinde, Klin. Wchnschr. **6**:1326, 1927.

33. Coelho, E.: Les troubles cardiaques dans la maladie de Basedow et le myxoedème, Ann. de méd. **30**:3, 1931.

34. Luten, D.: Myxedema with Partial Heart Block and Severe Anemia Both of Which Disappeared Under Thyroid Therapy, J. Missouri M. A. **26**:73, 1920.

35. Aub, J. C., and Stern, N. S.: The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, Arch. Int. Med. **21**:130 (Jan.) 1918.

36. Blackford, J. M., and Willius, F. A.: Chronic Heart Block, Am. J. M. Sc. **154**:585, 1917.

37. Drake, E. H.: A Case of Complete Heart Block with Interesting Reaction to Drugs, Am. Heart J. **31**:560, 1928.

block. Willius³⁸ reported two cases of myxedematous bradycardia, one showing a complete heart block and the other a sinus bradycardia, both with the Adams-Stokes syndrome. The patients were treated with thyroxin, U. S. P., and in each case the symptoms of the syndrome disappeared.

The possibility of a direct association between cardiac pain and myxedema was suggested in a communication by Hertoghe³⁹ in 1914. He thought that pain was due to myxedematous infiltration of the nerve cells of the supporting connective tissue. He also considered the possibility of cardiac pain resulting from too vigorous treatment with thyroid. Sturgis and Whiting⁴⁰ and Sturgis⁴¹ suggested that arteriosclerosis is a factor in the causation of angina pectoris, but he expressed the belief that anemia is of extreme importance because of the resulting added strain on the heart. Means, White and Krantz,²⁹ on the other hand, thought that anemia is not an important factor since there is not much acceleration of the blood flow in anemia. In their opinion, the attacks of angina pectoris may be the result of thyroid therapy, particularly in the cases associated with arteriosclerosis. Abrami, Brule and Heitz⁴² agreed with this theory. In contrast, Laubry, Mussio-Fournier and Walser⁴³ were of the opinion that the arteriosclerosis plays a possible part in the production of angina pectoris, but they thought that the angina is functional in origin since it responds so well to treatment. They also discussed the possibility of its being related to hypotonicity of the myocardium. Likewise, Ziskin⁴⁴ reported a case of myxedema heart associated with angina pectoris in which disappearance of the latter symptoms followed treatment. Finally, Blumgart, Gargill and Gilligan⁴⁵ suggested that the pain results from an increased flow of the blood following thyroid therapy, especially in cases in which there is arteriosclerotic narrowing of the coronary vessels.

38. Willius, F. A.: Thyroid Preparations in the Treatment of the Stokes-Adams Syndrome, *Canad. M. A. J.* **14**:1072, 1924.

39. Hertoghe, E.: Thyroid Deficiency, *M. Rec.* **86**:489, 1914.

40. Sturgis, C. C., and Whiting, W. B.: The Treatment and Prognosis in Myxedema, *J. A. M. A.* **85**:2013 (Dec. 26) 1925.

41. Sturgis, C. C.: Angina Pectoris as a Complication in Myxedema and Exophthalmic Goitre, *Boston M. & S. J.* **195**:351, 1926.

42. Abrami, P.; Brule, M., and Heitz, J.: Deux cas d'angine de poitrine avec myxoedème. Aggravation de l'hypertension par l'opothérapie, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:712, 1925.

43. Laubry, C., Mussio-Fournier, and Walser, J.: Syndrome angineux et insuffisance thyroïdienne, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1592, 1924.

44. Ziskin, T.: Angina Pectoris Associated with Myxedema Heart, *U. S. Vet. Bur. M. Bull.* **6**:24, 1930.

45. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. C.: Studies on the Velocity of Blood Flow, *J. Clin. Investigation* **9**:1, 1930.

There is little mention in the literature concerning the relationship between myxedema and hypertension. Means and Richardson^{13a} stated that hypertension may exist with, but is not a part of, myxedema. Abrami, Brule and Heitz¹² reported two cases in which the hypertension was increased as a result of thyroid treatment, and Duden^{2f} reported a case of myxedema in which an elevated blood pressure returned to normal following treatment.

The relation of thyroid therapy to edema in cases of myxedema has received some attention. Wenckebach⁴⁶ stated that in myxedema there is retention of water as a consequence of the insufficient thyroid secretion and that the water is expelled by thyroid treatment. March⁴⁷ expressed the belief that in his cases no disease of the heart or kidney was present, but that the ascites and peripheral edema, which cleared up with thyroid medication, were the result of the myxedema itself. Sainton, Doumer and V éran⁴⁸ stated that certain cases of cardiorenal disease are merely cases of hypothyroidism with edema, associated with renal failure, which respond very well to thyroid treatment.

Mention was made in the opening paragraph that the lack of unanimity of opinion as to this problem included not only clinical but pathologic and physiologic studies as well. Ord,⁴⁹ in 1880, described the pathologic findings in a case of myxedema. The heart was hypertrophied, flabby and dilated, and on section the heart muscle showed the connective tissue swollen and abundant and a great excess of mucin yielding interstitial cement. Similar changes were reported in the transactions of the clinical society of London in 1888⁵⁰ and by deBarry in 1899.⁵¹ In a case reported by Fishberg,⁵² the myocardium exhibited small scars and atheromatous changes in the large blood vessels and in the coronary arteries. Schultz⁵³ found a peculiar edematous swelling of the aortic leaflets, marked changes in the nuclei and granular degenera-

46. Wenckebach, K.: Heart and Circulation in a Tropical Avitaminosis (Beriberi), *Lancet* **2**:265, 1928.

47. March, H. E.: Myxedematous Ascites Removed by Thyroid Extract, *Am. J. M. Sc.* **172**:585, 1926.

48. Sainton, P.; Doumer, E., and V éran, P.: Syndrome cardio-r énal et hypothyroïdie, *Ann. de m é d.* **24**:513, 1928.

49. Ord, W. M.: Cases of Myxedema, *Tr. Clin. Soc. London* **13**:15, 1880.

50. Report of a Committee of the Clinical Society of London, *Tr. Clin. Soc. London*, 1888, supp. vol. 21.

51. deBarry, J.: Rachitischer Zwergwuchs, Endocarditis chronica, das Bild infantilen Myxödems vort äuschend, *Arch. f. Kinderh.* **26**:253, 1899.

52. Fishberg, A. M.: Arteriosclerosis in Thyroid Deficiency, *J. A. M. A.* **82**:463 (Feb. 9) 1924.

53. Schultz, A.: Ueber einen Fall von Athyreosis congenita (Myxödem) mit besonderer Berücksichtigung der dabei beobachteten Muskelveränderungen, *Virchows Arch. f. path. Anat.* **232**:302, 1921.

tion of the heart fibers. He did not find mucoid degeneration, but he was sure of the presence of edema between the fibers. Eppinger²³ spoke of fragile and brittle hearts with small scattered scars of the myocardium. Scholz⁵⁴ considered the pathologic changes in the heart in myxedema as merely incidental.

Tatum,⁵⁵ Benson,⁵⁶ Pick and Pinelas,⁵⁷ Horsley⁵⁸ and Goldberg,⁵⁹ working on thyroidectomized animals (rabbits, dogs, cats, sheep and goats), noted in some instances degeneration of the individual muscle fibers of the myocardium and edema of the interfibrillar tissues; in others, dilated hearts with a pale, flabby myocardium, and in others, evidence of pathologic changes in the pericardial sac. Goldberg⁵⁹ concluded that "the number of animals and the constant results obtained, also the fact that similar changes are observed in human cretins, make it almost certain that the organ changes found in these animals are the results of thyroidectomy." On the contrary, Kishi⁶⁰ and Brooks, Harlow and Larkin⁶¹ concluded from their postmortem studies on animals that the cardiac signs and symptoms produced as a result of hypothyroidism were not due to alterations in the heart muscle.

In the field of experimental physiology, interest has centered chiefly on a study of the electrocardiographic changes in thyroidectomized animals. After total thyroidectomy on dogs, Coelho³³ noted changes in the electrocardiogram similar to those reported by Zondek. Burlage⁶² made similar observations on his experimental cretin lambs. In contrast, Lueg,⁸ who used thyroidectomized dogs, lambs, goats and rabbits, failed to find changes in the electrocardiogram such as are found in myxedema in man.

54. Scholz, W., Myxödem, in Kraus, F., and Brugsch, T.: *Spezielle Pathologie und Therapie inneren Krankheiten*, Berlin, Urban & Schwarzenberg, 1919.

55. Tatum, A. L.: *Morphological Studies in Experimental Cretinism*, J. Exper. Med. **17**:636, 1913.

56. Benson, W.: Beitrag zur Kenntnis der Organveränderungen nach Schilddrüsen Extirpation bei Kaninchen, *Virchows Arch. f. path. Anat.* **170**:229, 1902.

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58. Horsley, V.: The Thyroid Gland: Its Relation to the Pathology of Myxedema and Cretinism, *Brit. M. J.* **1**:211, 1885.

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60. Kishi, K.: Beiträge zur Physiologie der Schilddrüse, *Virchows Arch. f. path. Anat.* **176**:260, 1904.

61. Brooks, Harlow, and Larkin, J.: A Brief Experimental Study of the Morphology of the Heart Muscle Following Hypothyroidism, *Am. J. M. Sc.* **155**:66, 1918.

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CLINICAL OBSERVATIONS

Our observations are based on a study of thirty-five cases of myxedema seen in the clinic for patients with diseases of the thyroid gland at the Boston City Hospital during the past seven years. The method of study was as follows:

After the diagnosis of myxedema was definitely established both clinically and by basal metabolic tests, roentgen plates were taken of the heart at a distance of 7 feet, and electrocardiograms were made. In the latter we noted the rhythm, rate, time of conduction, direction and amplitudes of the complexes. Treatment was then begun, and in a majority of cases thyroid tablets made from the fresh glandular material were prescribed. Whenever possible, basal metabolic tests, roentgen examinations and electrocardiograms were made at frequent intervals. The blood pressure readings were also noted. Fluoroscopic studies were made as often as possible.

In view of the fact that we were dealing largely with outpatients, it was not always possible to secure proper cooperation. Several patients did not return for treatment after the diagnostic studies were made, and others did not return for proper follow-up studies after treatment was instituted.

The results of our studies are given in tables 1, 2 and 3. For the sake of brevity, we have included in these tables only those cases showing changes in the electrocardiogram. Cases 30, 31 and 33 are not included in the statistical survey, for reasons to be mentioned later.

Summary of Findings in Tables.—The basal metabolic rates ranged from -12 to -59 , with an average rate of -33 . The P waves were low in all but one case. The T waves were low, flat or inverted, in every case returning to the normal deflection after the administration of thyroid (fig. 1). Increased P R intervals were present in four of the cases. In three, the conduction time returned to normal following treatment (fig. 2), whereas in the fourth there was an increase in time. The amplitudes of the R waves ranged from 3 to 8 mm., with an increase in height in each case following therapy. Three cases presented convex ST intervals, which returned to normal after treatment (fig. 3). One patient (case 6) discontinued her treatment, and the electrocardiogram showed a complete return to the abnormal type. With resumption of the thyroid therapy, the normal tracing was again seen. In seven cases there was enlargement of the heart, particularly to the left. As a result of the treatment, three cases showed a return to normal, two a diminution in size and one, no change at all. Two of the patients were subjected to fluoroscopic examination; they showed, in addition to the dilatation, markedly diminished pulsations of the heart. There was not much change in size, but a definite increase of the cardiac excursions was noted very soon after treatment was instituted. In patient 34 there developed, while in the hospital, a hydropneumothorax with no apparent

TABLE 1.—Findings in Thirteen Cases of Myxedema

Case	Sex	Age	Basal Meta- bolic Rate	Comment	Electrocardiogram					Comment	Roentgenogram	Blood Pressure		
					Rhythm Rate *	P Waves	T ₁	T ₂	T ₃			Axis Ampl.	Sys- tole	Dias- tole
1	F	35	-37	Before treatment	N.S.R. 73	Norm.	Inverted	Norm.	Norm.	LVP 5	Normal, Tr.d., 12.8			
28	F	42	-43	Before treatment	N.S.R. 100	Flat	Inverted	Flat	Flat	Norm. 5	Enlarged, Tr.d., 15.6	122	86	
10	F	54	-22 -22 + 4	6 yrs. after treatment began 9 mos. later 7 wks. after last treatment	N.S.R. 91 N.S.R. 73 N.S.R. 83	Low Low Norm.	Flat Flat Norm.	Flat Flat Norm.	Flat Flat Inverted	Norm. 5 LVP 6 LVP 13	Normal	160 140 80	90 80	
17	F	40	-20 - 8	1 yr. after treatment began 3 yrs. after last treatment	N.S.R. 70 N.S.R. 83	Low Norm.	Inverted Norm.	Inverted Norm.	Inverted Flat	LVP 6 Norm. 10	Normal	90 122	70 70	
6	F	42	-43 -34 +17 -34	Before treatment 4 days after treatment 15 days after treatment 27 days after treatment No treatment for 2 mos. 1 mo. after treatment began	N.S.R. 90 N.S.R. 95 S.A.T. 133 S.A.T. 120 N.S.R. 88 S.A. 80	Low Norm. Norm. Norm. Low Norm.	Flat Norm. Norm. Norm. Flat Norm.	Flat Norm. Norm. Inverted Norm.	Inverted Inverted Inverted Inverted Inverted Inverted	Norm. 3 Norm. 5 Norm. 7 Norm. 10 Norm. 6 Norm. 7	Enlarged, Tr.d., 14.3 Normal, Tr.d., 11 Normal	112 102	68 60	
20	F	27	-59 -14	Before treatment 9 mos. after treatment	N.S.R. 79 N.S.R. 71	Low Norm.	Flat Norm.	Low Norm.	Low Norm.	Norm. 7 Norm. 11	Enlarged, Tr.d., 15 Normal, Tr.d., 13.8	100 124	70 70	
26	M	62	-26 - 2	Before treatment 2½ mos. after treatment	N.S.R. 79 N.S.R. 79	Low Norm.	Low Norm.	Low Norm.	Flat Norm.	Norm. 6 Norm. 10	Normal, Tr.d., 13.9	158	104	
29	F	58	-35 -20 + 4	Before treatment 6 days after treatment 15 days after treatment	N.S.R. 63 N.S.R. 71 N.S.R. 79	Low Norm. Norm.	Inverted Norm. Norm.	Inverted Norm. Norm.	Inverted Flat Norm.	LVP 5 LVP 5 LVP 10	Enlarged, Tr.d., 16.3 Normal, Tr.d., 12.2	104 112	62 66	
32	M	60	-35 + 5	Before treatment 3 wks. after treatment	S.B. N.S.R. 75	Low Norm.	Flat Norm.	Flat Norm.	Flat Norm.	Norm. 8 Norm. 9	High resist- ance	Enlarged, Tr.d., 17.8 Enlarged, Tr.d., 17.6	104 108	70 62
34	F	72 -12 -10	Before treatment (4/23/32) 4/27/32 5/4/32 5/10/32 Started on treatment 5/16/32 5/17/32 S.A. 52 Low Flat Flat Flat Norm. 4.5	Enlarged to left Sclerotic arch P R 0.26	110	70	
					N.S.R. 61	Low	Low	Inverted	Inverted	LVP 6	Fluoroscopy †			
					Fluoroscopy †			

	- 6	5/21/32 5/25/32	N.S.R. 65	Low	Diphasic	Diphasic	Flat	LVP 6	P R 0.24	Enlarged, Tr.d., 14.6 Fluoroscopy †
	+ 5	5/23/32 6/ 2/32	S.A. 80	Norm.	Diphasic	Low	Flat	LVP 7	P R 0.24	Normal, Tr.d., 12.7 Fluoroscopy †
	+ 8	6/ 5/32 6/10/32 6/13/32 6/20/32 6/22/32	S.A. 80 N.S.R. 100 N.S.R. 95	Norm. Norm. Norm. Norm.	Low Norm. Low	Norm. Norm. Norm.	Flat Flat Norm.	LVP 7 LVP 5.5 LVP 7	P R 0.22 P R 0.22 P R 0.20 Normal, Tr.d., 13.4 Normal, Tr.d., 13
F 37	-31	Before treatment	S.A. 85	Low	Flat	Inverted	Inverted	Norm. 8	Convex S T	None
	-18	3 mos. after treatment	S.A.T. 110	Low	Flat	Flat	Flat	Norm. 6	Norm. S T
	+ 7	5 mos. after treatment	S.A.T. 111	Norm.	Norm.	Norm.	Flat	Norm. 10	Normal, Tr.d., 13.4
		8 mos. after treatment	S.A. 88	Norm.	Norm.	Norm.	Inverted	Norm. 9	
F 50	Before treatment	N.S.R. 60	Low	Flat	Inverted	Inverted	Norm. 4	Enlarged, Tr.d., 20 (40 inch distance)
	-30	(5/ 5/32) 5/10/32	Fluoroscopy †
	-26	Started on treatment	N.S.R. 58	Low	Flat	Diphasic	LVP 5	Enlarged, Tr.d., 19.9 (40 inch distance)
	-20	5/23/32 5/25/32 5/28/32 6/ 2/32	N.S.R. 60	Low	Flat	Inverted	Norm. 4.5	(7 ft.) Tr.d., 17.7 Fluoroscopy †
			Enlarged, Tr.d., 17.8 Fluoroscopy †
	-18	6/ 5/32 6/10/32 6/14/32 6/23/32	S.A. 67 N.S.R. 68 N.S.R. 60	Norm. Norm. Norm.	Low Norm. Norm.	Flat Low Flat	Inverted Inverted Inverted	Norm. 5 LVP 6 LVP 8 Enlarged, Tr.d., 16.2
	-11		
F 60	-31	Before treatment	N.S.R. 60	Norm.	Inverted	Inverted	Norm.	LVP 12	Convex S T	Normal, Tr.d., 11
	+11	Months after treatment	N.S.R. 79	Norm.	Inverted	Inverted	Norm.	LVP 18	Convex S T	Enlarged, Tr.d., 17.6

* N.S.R. = normal sinus rhythm. S.A. = sinus arrhythmia. S.A.T. = sino-auricular tachycardia. S.B. = sinus bradycardia. Norm. = normal amplitude and direction of waves. LVP = left ventricular predominance. Ampl. = amplitude of R wave in its highest lead. Tr.d. = transverse distance.

† 5/10/32: Small hydropneumothorax on right side of heart, transversely enlarged. Pulsation of heart markedly diminished in intensity and excursion.

5/17/32: Fluid still present. Heart enlarged to left. Pulsations definitely increased over those of previous record but still below normal.

5/25/32: Small amount of fluid at left base. Heart slightly enlarged. Pulsations still further increased in intensity.

6/ 2/32: Fluid gone. Heart slightly enlarged to left. Pulsations normal in intensity and excursion.

† 5/10/32: Excursion of diaphragms limited. Supracardiac area increased. Heart enlarged transversely. Pulsations markedly diminished; at times imperceptible.

5/28/32: Heart enlarged transversely. Pulsations markedly increased over those on previous examination, but still below normal limits.

6/ 2/32: Heart still enlarged transversely. Pulsations of heart now within normal limits.

cause. This condition cleared up entirely when the patient received thyroid medication. Before treatment, the systolic blood pressure ranged from 90 to 160 with an average of 120; following treatment the average reading was 117.

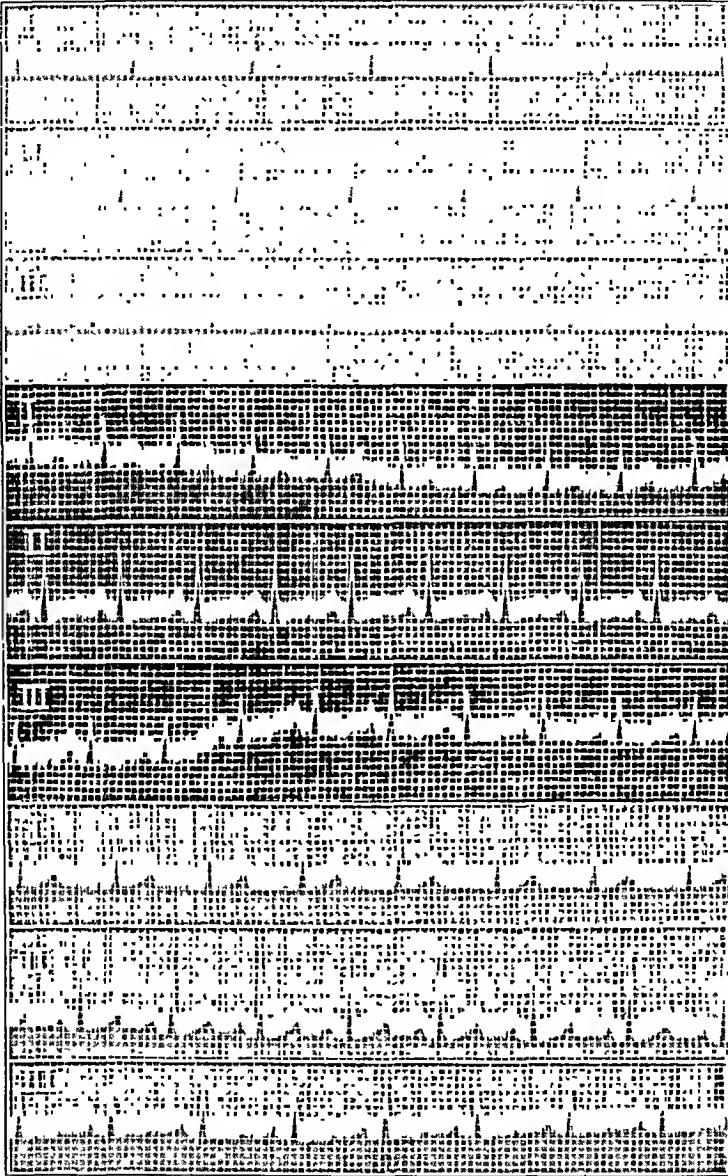


Fig. 1 (case 6).—The first set (at top) was taken before treatment; the second set fifteen days, and the last set one month, after the beginning of treatment.

Case 30 is mentioned in a separate paragraph in view of the fact that the electrocardiographic picture was different from all those studied. There was normal amplitude of all the complexes. Under intensive thyroid treatment there was a disappearance of all the symptoms of myxedema, with a corresponding rise in the basal metabolic rate and no essential change in the electrocardiographic tracing (fig. 4).

This patient first came to the clinic in 1924 for treatment of myxedema. It was not until four years later that any change in cardiac rhythm was noted. This was diagnosed as bradycardia with many extrasystoles, and the first electrocardiogram was not made until a year later ;

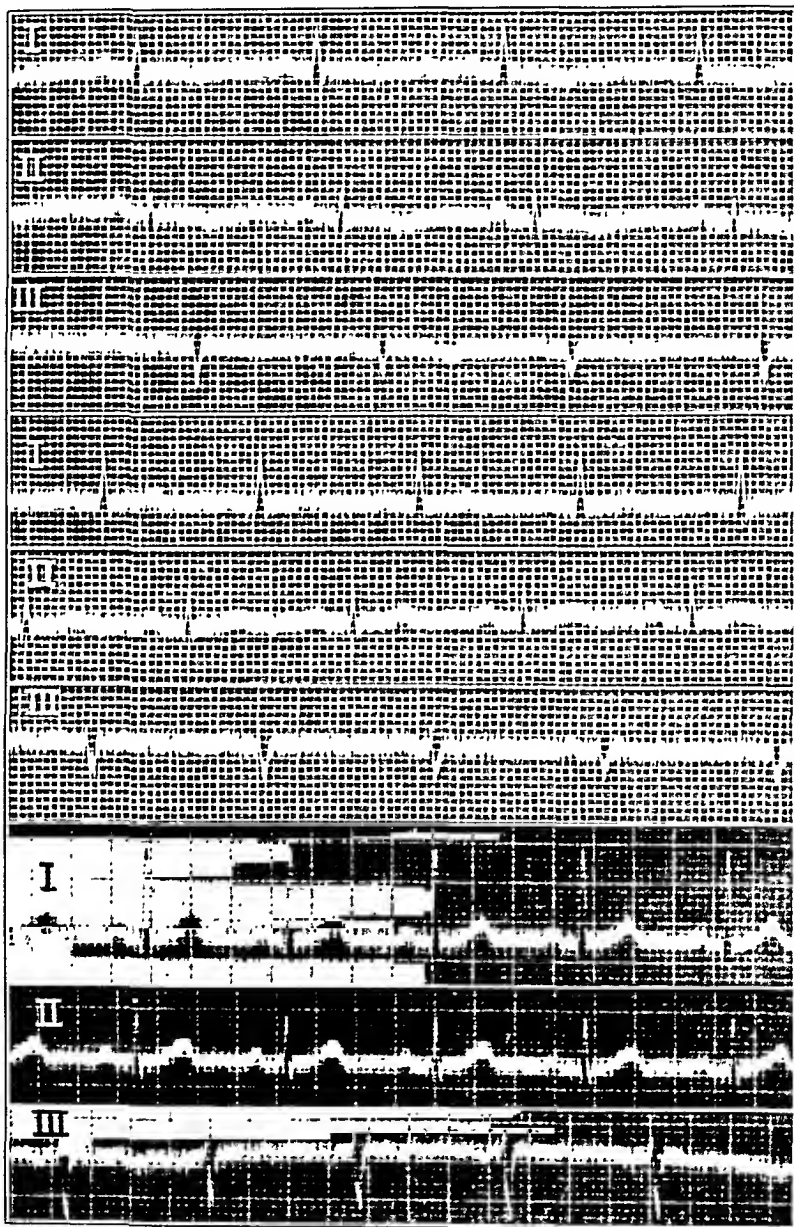


Fig. 2 (case 29).—The first set was taken before treatment; the second set six days, and the last set fifteen days, after treatment was started.

the report may be examined in table 2. At this time, in addition to thyroid medication digitalis was given, but when the fibrillation disappeared, the administration of digitalis was discontinued. However, the patient continued to show various abnormalities of rhythm, predominantly a marked sinus arrhythmia with a slow rate. Following treatment

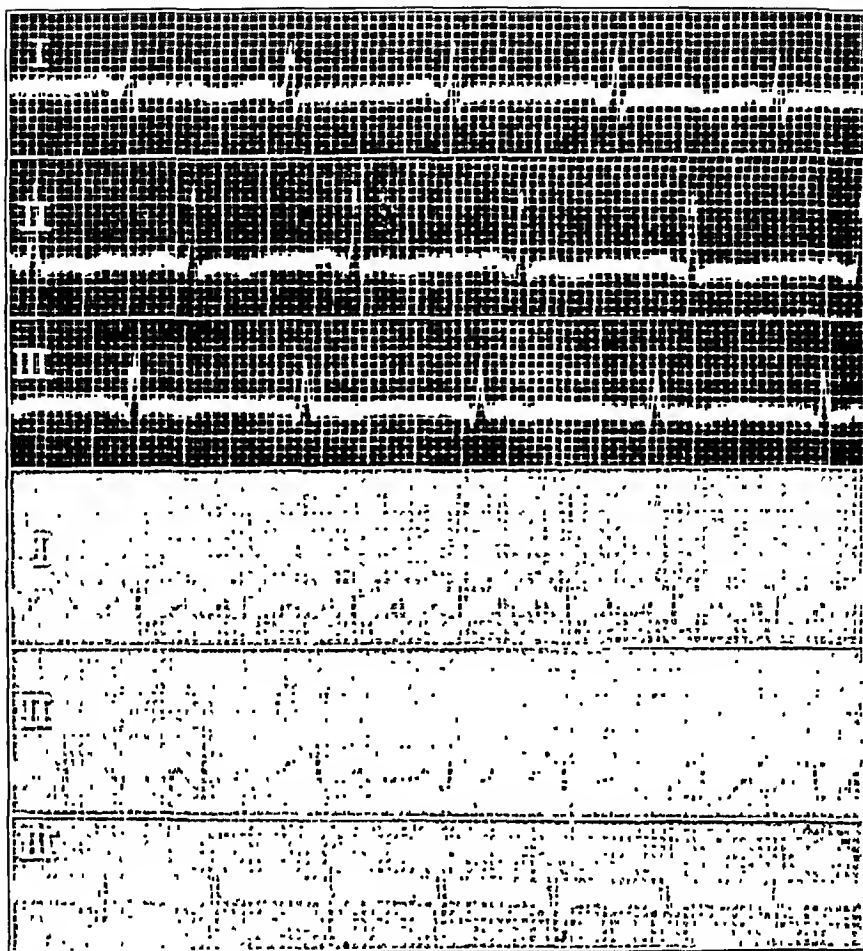


Fig. 3 (case 11).—The upper set was taken before treatment; the lower set, five months after the onset of therapy.

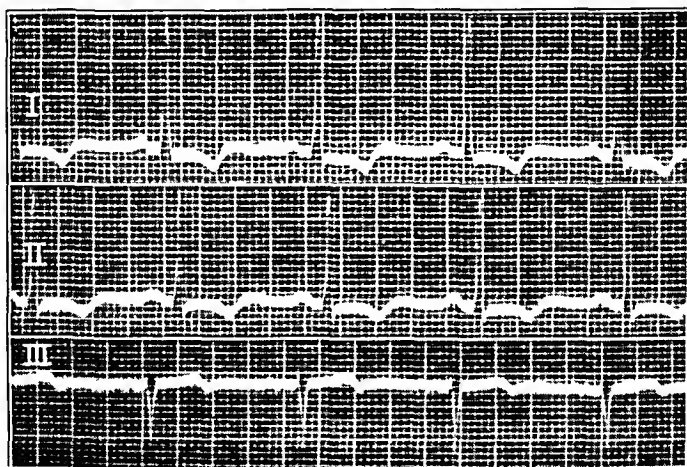


Fig. 4.—Tracings in case 30.

with thyroid there was a decrease in blood pressure from 148 systolic and 100 diastolic to 120 systolic and 60 diastolic.

In case 31 (table 3) in spite of the moderately low metabolic rate the patient presented a rather typical picture of myxedema. She was treated with thyroid extract. She gave a history of attacks of paroxysmal tachycardia over a period of many years, but we have no records confirming these previous seizures, and it was not until she had omitted her treatment for a period of three months that our first tracing was obtained. Four electrocardiograms were taken in the interval when she received no therapy; two of these were made during attacks of tachycardia.

It is to be noted that there was a gradual change in the T waves with a tendency toward inversion, which ultimately occurred in all the leads during the period in which the patient received no treatment. The conversion from a normal axis to a left ventricular predominance is also noted. However, no essential change was observed in the amplitude.

Eight months after reinstitution of treatment, a normal electrocardiogram and a low basal metabolic rate were obtained. Shortly following this, the patient again neglected her treatment, taking the thyroid preparation at more or less irregular intervals. The last tracing recorded shows the picture five months later, at which time she presented practically the same clinical picture of myxedema as at the onset. Unfortunately, no basal metabolic rate was obtained at this time.

According to the roentgen-ray examination, the heart was slightly enlarged when the patient had had no treatment for three months; six months later when she still received no thyroid medication it was within normal limits. A moderate hypotension was present both before and after the treatment.

GENERAL SUMMARY OF FINDINGS

Electrocardiographic Studies.—1. Incidence: There were twenty-one cases out of a total of thirty-five in which electrocardiograms were taken before treatment. Thirteen of these were of the type described by Zondek. The average age of the patients showing changes in the electrocardiogram was 47. Three cases out of the entire group developed myxedema following subtotal thyroidectomy. Two of these cases are represented in the group showing changes in the electrocardiograms and in the size of the heart.

2. Relation to Basal Metabolic Rate: With three exceptions, we found that when the basal metabolic rate dropped to a level of -25 or lower, a definitely abnormal picture was seen in the electrocardiogram. These three exceptions were basal metabolic rates of -12 , -20 and -22.6

TABLE 3.—Data on a Woman Aged 39 (Case 31) *

Basal Metabolic Rate	Rhythm	Rate	Electrocardiograms					Roentgenogram of Heart at 7 Feet	Blood Pressure	
			T ₁	T ₂	T ₃	Axis	Ampl.		Systolic	Diastolic
-17	100	50
	Paroxysmal auricular tachycardia	200	Norm.	Norm.	Norm.	Norm.	8	Heart and great blood vessels slightly enlarged	102	70
	Marked sinus arrhythmia	50	Norm.	Diphasic	Inverted	Norm.	11	1 week later		
	Paroxysmal auricular tachycardia	200	LVP	8	6 months later	Heart within normal limits	
-24.5	Normal sinus rhythm	79	Inverted	Inverted	Inverted	LVP	10	1 week later		
-30	Normal sinus rhythm	68	Norm.	Norm.	Inverted	LVP	13	8 months after treatment began		
	Normal sinus rhythm	71	Low	Diphasic	Inverted	Norm.	5	Treatment irregular		

* For meaning of abbreviations see table 1.

3. Characteristics of the Tracings: In general, abnormalities noted were of the type described by Zondek.

The decreased height of the R wave was a rather constant finding. With the exception of one case in which the amplitude was artificially greater, owing to high resistance, the height was 7 mm. or less. (In the opinion of Pardee,⁶³ the height of the R wave varies from 7 to 16 mm. Willius⁶⁴ recorded the height as varying between 10 and 16 mm. In our series we have considered low voltage present when the R wave was less than 8 mm.) There seemed to be a parallelism between the basal metabolic rate and the height of the R wave; that is, in any one case when there was an increase in the level of the basal metabolic rate under thyroid therapy, the amplitude of the R wave increased also. However, the level of any given basal metabolic rate does not indicate the exact height of the R wave. For example, in case 20, with an initial basal metabolic rate of —59, the maximum amplitude of the R wave was 7 mm., while in case 6, with a basal metabolic rate of —43, the amplitude was 3 mm.

We denote low T waves when their amplitude is lower than 3 mm., which according to Willius is the lowest level of normalcy. Our results are tabulated as follows:

	Normal	Low	Flat	Inverted
T ₁	0	1	7	5
T ₂	1	2	5	5
T ₃	1	1	5	6

Thus it is seen that the T waves in all leads show parallel results. It is noteworthy that the T waves in lead I were abnormal in every case. Generally speaking, the lower the amplitude of the R wave, the greater was the tendency for the T waves to be flat, and in some cases these waves, particularly in lead II, became inverted during the progress of treatment before a final rise to the upright position. In two cases the T wave in lead III, which was flat before treatment, became inverted under thyroid medication and remained so. This was probably the normal deflection for those patients. The amplitude of negative T waves in any or in all of the leads may be as much as 2 or 3 mm., even in the presence of extremely low voltage in the other waves.

Size of Heart.—Enlargement of the heart occurred in seven of the thirteen cases showing electrocardiographic changes. With one exception, the increased size of the heart was reduced as a result of thyroid therapy. The failure mentioned may be due to the fact that the treatment was carried out for only three weeks.

63. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, New York, Paul B. Hoeber, Inc., 1928.

64. Willius, F. A.: *Clinical Electrocardiograms*, Philadelphia, W. B. Saunders Company, 1929.

Blood Pressure.—No characteristic changes in blood pressure were observed. In the presence of cardiac dilatation the blood pressure was found to be normal or subnormal. In those cases in which the pressure was particularly low it tended to rise under treatment. In cases in which hypertension was present the pressure tended to decrease under thyroid therapy. This last observation was made by Ohler and Ullian⁶⁵ in a previous report.

Pathologic Studies.—We have little or no pathologic material which would give us the true picture present in the heart in cases of myxedema. There was, however, one case (table 1, case 28) which presented the clinical picture of the so-called myxedema heart. The patient died an accidental death before thyroid therapy was instituted. Unfortunately, no microscopic studies were made. The heart weighed 335 Gm. There were edema of the epicardial fat and a translucent, light red heart muscle. The mitral valve showed some old thickening of the anterior flap with thickening and shortening of the chordae tendineae. The aortic arch showed irregular bands of small yellow projections running longitudinally with a few small gray-white opaque scars. The thyroid gland was represented by a thin structure separated into two lobes, almost membranous in places and without an isthmus. Section disclosed gray soft tissue having little resemblance to normal thyroid gland tissue.

Symptoms and Physical Signs.—Shortness of breath was a complaint present in almost every case of myxedema studied. Many patients complained of palpitation, and a few experienced precordial pain. These symptoms occurred as frequently in the cases not showing changes in the electrocardiogram and roentgenogram as in those that did. Edema of the lower extremities was found without respect to cardiac changes, but was more marked in the cases showing cardiac enlargement. Pulmonary congestion was found only in cases with cardiac enlargement, but this finding was not constant.

Treatment.—This consisted of administration of fresh thyroid gland extract. No attempt was made to quantify the required amount of thyroid by comparison with the metabolic rate. In general, treatment was begun slowly and was gradually increased until there was a disappearance of all symptoms subjectively and objectively, with a return to the normal picture in the electrocardiogram. The last dose was considered a maintenance requirement. In some cases it was noted that the electrocardiographic changes occurred before the basal metabolic rate had risen to normal limits. In such cases it was our practice not to increase the dose in an attempt to raise the metabolic rate.

65. Ohler, W. R., and Ullian, L. J.: Clinical Survey of 1,000 Cases on Whom Basal Metabolism Studies Have Been Made, *M. Clin. North America* 8:1495 (March) 1925.

COMMENT

In a review of the literature, we find numerous subjects concerning the cause of such cardiac changes as may be found in myxedema. It is our intention now to review the more important of these subjects in the light of our own study.

Changes in the Electrocardiogram.—1. Sclerosis of the Coronary Arteries: There is a very close resemblance between the variations in the electrocardiogram found in our cases of myxedema and the picture not infrequently seen in coronary sclerosis as originally described by Pardee.¹⁶ The low voltage, the inverted T waves and the upward convexity of the S T interval are findings common to both diseases. But in our cases of myxedema, the amplitude was constantly low, while in coronary sclerosis, the height of the complexes, though frequently low, may be very high. Many of our patients showed no evidence of peripheral arteriosclerosis, and in those who did have thickened arteries there was no change in the vessels after years of treatment. The influence of arteriosclerosis is well demonstrated in one of our cases (30). In spite of the definite myxedematous syndrome, the amplitude of all the complexes was quite high, and there was marked inversion of the T waves. Had these abnormalities been due to myxedema, we should have expected to find changes, at least in the T wave, following thyroid therapy, but such was not the case. Thyroid medication had no more effect than it does on the electrocardiographic changes seen in uncomplicated coronary sclerosis. We also believe that the changes observed in the electrocardiograms of the patient referred to in table 2 were due to arteriosclerosis of the coronary arteries. Here, also, following thyroid therapy no effect was noted, not even on the bradycardia.

2. Anemia: In view of the fact that in most cases of myxedema there is at least a moderate degree of secondary anemia, the theory that the electrocardiographic changes are due to associated anemia of the myocardium cannot be dismissed lightly. Yet, according to the observations of Dr. Lawrence Ellis,⁶⁶ of the Boston City Hospital, in a series of cases of anemia no characteristic changes were noted in the electrocardiogram. Also, the results in one of our cases (34) tend to disprove the theory of anemia. On the patient's admission, the electrocardiogram showed a definitely abnormal tracing, and the blood picture was fairly normal. In the course of a few weeks there developed a well marked secondary anemia due to bleeding from the gastro-intestinal tract. Nevertheless, during this time the electrocardiogram became normal as a result of thyroid therapy. Of course, it may be argued that there is a local ischemia of the myocardium in myxedema, the determination of which is a problem yet to be solved.

66. Ellis, L. B.: Personal communication to the authors.

3. Cardiac Dilatation and Sluggishness: Can dilatation of the heart be said to account for the electrocardiographic changes? We do not believe so, in view of the fact that in several of our cases roentgenograms revealed no enlargement. Likewise, sluggishness of the myocardial contractions as a cause seems unlikely if we consider that in one of our patients the cardiac action became definitely normal as seen on fluoroscopy while there was but little change in the electrocardiogram.

4. Nervous Etiology: Vagal stimulation, which is probably a part of the general picture of myxedema, has been considered as the factor producing changes in the electrocardiogram, including prolongation of the P R conduction time. It does not seem likely, however, that alteration in nerve conduction could cause any such great degree of dilatation of the heart as we see in myxedema.

5. Cutaneous Resistance: We do not believe that resistance of the skin can result in inversion of the T waves, nor can it account for prolongation of conduction time. It is our experience that when the resistance is experimentally increased by poor electrode contact the height of the complexes is increased rather than lowered if proper standardization is made.

6. Pericardial Effusion: Electrocardiographic changes similar to those observed in myxedema were noted in cases of pericardial effusion by Oppenheimer and Mann,⁶⁷ Master and Pardee⁶⁸ and Scherf.⁶⁹ Cases of pericardial effusion with typical coronary T waves, but without diminution of the voltage, were reported by Purks⁷⁰ and Scott, Feil and Katz.⁷¹ Also Gordon⁷² described cases of pericardial effusion showing the characteristic picture of the heart in myxedema with a return to normal following the removal of the effusion. Gager⁷³ has described a case (no basal metabolic studies) of pericardial effusion which showed the "myxedema tracing," together with partial heart block. Following

67. Oppenheimer, B. S., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, *Proc. Soc. Exper. Biol. & Med.* **20**:431, 1922.

68. Master, A. W., and Pardee, H. E. B.: The Effect of Heart Muscle Disease on the Electrocardiogram, *Arch. Int. Med.* **37**:1 (Jan.) 1926.

69. Scherf, D.: Ein elektrokardiographisches Zeichen bei Erguss im Herzbeutel, *Wien. klin. Wchnschr.* **43**:298, 1930.

70. Purks, W. K.: The Occurrence of a Coronary T-Wave in Purulent Pericarditis, *South. M. J.* **24**:12, 1931.

71. Scott, R. W.; Feil, H., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion, *Am. Heart J.* **5**:68, 1929.

72. Gordon, A. H.: Some Clinical Aspects of Hypothyroidism, *Canad. M. A. J.* **20**:7, 1929.

73. Gager, L. T.: Conduction Changes Accompanying Pericardial Effusion, *Arch. Int. Med.* **33**:449 (April) 1924.

the removal of 500 cubic centimeters of fluid from the pericardial sac, the electrocardiogram became normal, and the partial block disappeared. It is true that pericardial effusion may occur in myxedema, but it was not the cause of the changes in the electrocardiogram in our series of cases, as in only one case was there a suspicion of pericardial effusion on fluoroscopic and roentgenographic examination (case 33). Moreover, the fact that in general the cardiac pulsations return to normal under thyroid therapy with very little change in the size of the heart would seem to preclude the likelihood of the presence of an effusion.

In our opinion, none of the theories reviewed serves as an adequate explanation. Unfortunately, in our own studies, we have been unable to discover the actual underlying basis for the electrocardiographic changes. We might advance the theory already suggested, that of the presence of an actual myxedematous infiltration of the heart, a mucinous tissue involving the muscular fibers and interfibrillar spaces and nervous elements of the heart, which disappears under thyroid therapy. It may be that this abnormal tissue is present in some cases in such a small quantity as merely to produce changes in the electrical activity, evidenced by abnormalities in the electrocardiogram, without changes in the actual size of the heart, whereas in other cases there may be a sufficient quantity to cause dilatation. The test of this theory awaits more detailed pathologic study, either of man or of experimental animals.

Dangers of Treatment.—The dangers of uncontrolled thyroid treatment have been stressed by numerous writers. We should like to report here a case which has come to our attention and which, in our opinion, illustrates this point quite definitely. The patient was a man, aged 30, who when first seen had edema of the lower extremities and a basal metabolic rate of -21 . He was given 15 grains (0.972 Gm.) of desiccated thyroid gland daily for the first few days, then 30 grains (1.95 Gm.) a day for a few days, and then he was allowed to go home, continuing on a dose of 15 grains (0.972 Gm.) a day. During the course of this treatment, the edema entirely disappeared. The effect of treatment in this case was not checked by electrocardiographic or metabolic studies. Four days after discharge, the patient, while at home, suddenly complained of severe pain in his left shoulder; he dropped to the floor, and in one-half hour was pronounced dead. It is our impression that this patient probably died in an attack of angina pectoris, due in part to the excessive amounts of thyroid administered.

Further dangers to be noted in the treatment of myxedema with thyroid gland extract are auricular fibrillation, as seen in a patient observed by Swan,⁷⁴ and Adams-Stokes attacks, as reported by Thomp-

• 74. Swan, J. M.: A Case of Auricular Fibrillation Occurring During the Administration of Thyroid Substance, *Ann. Clin. Med.* 3:311, 1924.

son.⁷⁵ In both of these cases, the untoward symptoms disappeared with the diminution of the dose of the drug.

SUMMARY

1. Thirty-five cases of myxedema were studied, thirteen of which showed abnormal changes in the electrocardiogram.

2. The characteristic changes in the electrocardiogram are a decrease in voltage of all the complexes and frequently an inversion of the T waves in all the leads. Increased auricular-ventricular conduction time is seen in some cases.

3. These abnormal electrocardiograms are seen with few exceptions when the basal metabolic rate drops to a level of —25 or lower.

4. Enlargement of the heart revealed by roentgenograms is seen frequently in cases showing abnormal electrocardiograms. Sluggishness of cardiac contractions is demonstrated by fluoroscopy.

5. The specificity of thyroid gland extract in these cases is shown, the electrocardiogram and the size of the heart returning to normal following treatment.

6. Low, normal and high blood pressures are seen in myxedema. In patients with dilated hearts the pressure tends to be normal or subnormal. In our series, thyroid treatment tended to increase the blood pressures that were low and to decrease those that were high.

7. Distant heart sounds and mild congestive failure are frequent clinical findings.

8. The changes noted in this series are characteristic of the disease and warrant the use of the term, "myxedema heart."

9. Attention is directed to the paucity of careful pathologic studies of the heart muscle in myxedema. A definite explanation of the cause of the cardiac changes in myxedema may not be possible until such a study is completed.

Dr. Joseph Hallisey, in charge of the outpatient cardiac clinic, gave permission for the study of cases in his service.

75. Thompson, W.: The Blood Volume in Myxedema with a Comparison of the Plasma Volume Changes in Myxedema and Cardiac Edema, *J. Clin. Investigation* 2:477, 1926.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

II. HEMOGLOBIN, HEMATOCRIT AND ERYTHROCYTE DETERMINATIONS AND TOTAL AMOUNT OF VARIATIONS OF EACH

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Many reports have been published of hemoglobin and erythrocyte determinations in pregnancy, and the accepted belief is generally that there is a decrease in both, producing an anemia which has been called the physiologic anemia of pregnancy. The hemoglobin and erythrocytes are decreased occasionally to such a degree that the anemia has been termed the pernicious anemia of pregnancy. Various theories have been advanced as to the cause of this disease. Some authors suggest excessive demands of the fetus for iron; others believe that there is a dietary cause on the part of the mother, and others that a hemolysin is produced by the syncytial cells. Irrespective of the cause of the severe anemia, the treatment is of paramount importance because the maternal and fetal mortalities are very high.

Balfour,¹ reporting 150 cases of severe anemia in pregnancy in India, stated that 42 per cent of the mothers and 68 per cent of the fetuses died. McSwiney² reported 43 cases, also in India, with a maternal mortality of 35 per cent and a fetal mortality of 56 per cent. Treatment has been varied, but all authors advise termination of the pregnancy. It seems strange that little or no work has been done on the etiology of a disease causing such a high mortality. The need for research in this disease is further indicated by some figures from the Chicago Lying-in Hospital. F. L. Adair instituted routine hemoglobin estimations, and in a six month period there were 1,176 new patients admitted to the clinic, of whom 268, or 23 per cent, had a hemoglobin content

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1. Balfour, M. I.: *Indian M. Gaz.* 62:491, 1927.

2. McSwiney, S. A.: *Indian M. Gaz.* 62:487, 1927.

under 10 Gm. The number of clinical patients with severe anemia in pregnancy is constantly increasing, owing, probably, to the economic situation. Work has been started to determine the etiology of this type of anemia.

However, before one can speak of a pernicious anemia or severe secondary anemia of pregnancy, the normal changes in hemoglobin and red blood cells incident to pregnancy must be known. All of the data which have been published, with but two exceptions, namely, those of Fehling,³ in 1886, and of Kühnel,⁴ in 1926, were obtained from a study of different groups of women during pregnancy, and because of the wide variations found normally, these data are inconclusive. Hemoglobin and hematocrit determinations and red blood cell counts on the same woman throughout pregnancy will show marked variations because of the changes in blood and plasma volumes. However, if the blood volume is determined, the total amount of hemoglobin and cells can be calculated, and the conversion of these figures to percentage of increase or decrease from certain designated standards will show definitely what effect pregnancy has on these blood constituents.

Kehrer,⁵ in his review of the literature to 1923, in the Halban and Seitz system, concluded that in the healthy pregnant woman the red blood cell count, as well as the content of hemoglobin, is near the upper limits of normal, and that especially during the last month there is an additional increase. He stated the belief that this is due to increased work of the hematopoietic organs, increased intake of food and less exercise during pregnancy.

DeLee⁶ stated:

Investigators are not agreed on the changes which the blood undergoes during pregnancy and it is because the blood reacts differently under the stimulus of pregnancy in different women. From external appearances, many women, especially those ill-nourished or living in poor circumstances, suffer from a condition of chloranemia. The fetus uses up a great deal of iron and calcium, but, normally, the blood lacks neither. While in the first few months there may be a reduction in the reds, the system soon reacts to the necessities imposed by pregnancy and there is an increase of the red.

Williams⁷ stated:

In former times it was generally believed that the changes incident to the placental circulation demanded an increase in the amount of maternal blood, and

3. Fehling: *Arch. f. Gynäk.* **28**:453, 1896.

4. Kühnel, P.: *Ztschr. f. Geburtsh. u. Gynäk.* **90**:511, 1927.

5. Kehrer, E., in Halban, Joseph, and Seitz, Ludwig: *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenberg, 1926, vol. 6, p. 778.

6. DeLee, J. B.: *Principles and Practice of Obstetrics*, Philadelphia, W. B. Saunders Company, 1928.

7. Williams, J. W.: *Obstetrics: Textbook for Use of Students and Practitioners*, New York, D. Appleton and Company, 1930.

all the earlier writers stated that under the influence of pregnancy an increased hydremia and a diminution in hemoglobin and red corpuscles took place, while at the same time an abnormal amount of fibrin could be noted. These observations were based upon antiquated methods of research, and it was not until 1886 that Fehling, by the aid of modern appliances for examining the blood, came to the conclusion that it underwent little, if any, change. Since then a number of articles have appeared, notably those of Payer and Dietrich, which show that in the later months of pregnancy the amount of hemoglobin and of red corpuscles is normal, or even slightly increased. Kühnel, however, speaks of a physiological anemia of pregnancy, and believes that normal conditions are not restored until some months after delivery. Extended, but as yet unpublished, observations by Harris⁸ in our service during 1922 and 1923, demonstrated that the volume of blood is definitely increased, while the cell and hemoglobin content is relatively, but not actually, diminished.

Kühnel⁴ made hemoglobin, red blood cell and hematocrit determinations in 15 women throughout pregnancy and the puerperium, and in a few cases for a year post partum. His minimum figures are given in table 1. The hemoglobin determinations were made with a Sahli hemoglobinometer, which was corrected three times during the investigation, but he did not mention how it was standardized. His determinations were made on citrated venous blood which was obtained after a thirty minute rest period, without stasis. The study was carefully controlled, and we believe that it is accurate, with the one exception of the hemoglobin determinations, in which there is, according to his own statement, an average error of 10 per cent; however, his conclusions are warranted because he followed the same patients with the same methods, and the error, presumably, was constant. In all of his patients, whether they were the robust, plethoric type, or the pale, less robust type, decreasing values were found for the three factors, and the diminution was so definite that one could speak of an anemia of pregnancy. The minimum figures (decrease in hemoglobin of 20 per cent, in cell volume of 17 per cent and in erythrocytes of 20 per cent) were reached at from the sixteenth to the twenty-second week and were maintained until the thirtieth to the thirty-second week; then there was a gradual rise, reaching a maximum at about thirty-four weeks; however, the normal was not reached. He stated that pregnancy causes a slowly disappearing chlorosis that lingers for months (usually still in evidence six months post partum), and he advised a proper diet in all cases of frequently recurring pregnancies.

Plass and Bogert⁹ determined the cell volume on groups of women at varying periods during pregnancy and the puerperium. Oxalate was used as an anticoagulant, and, presumably, the tourniquet was kept in place during the venipuncture. The average cell volume for nonpreg-

8. Harris, cited by Williams.⁷

9. Plass, E., and Bogert, L.: *Bull. Johns Hopkins Hosp.* **35**:361, 1924.

nant women was 39.5. In the first trimester it decreased to 35.6, and in the second it was 31.5, remaining at this level during the balance of the pregnancy. Three weeks post partum the cell volume was 34.7.

Skajaa¹⁰ determined cell volumes with venous blood at term, during labor and post partum in normal and in toxemic patients, using heparin or hirudin as the anticoagulant. He summarized his report as follows: During pregnancy the cell volume diminishes. In 120 normal women at term, the mean figure was 36.4, as against a mean of 44.4 in nonpregnant women. At term and during labor the cell volume in many cases shows great variations. These are due to variations in the quantity of plasma and accordingly indicate, respectively, a condensation (concentration) or a dilution of the blood as regards suspension of erythrocytes. In women without signs of toxemia the cell volume is unchanged in the last weeks before parturition, and during labor shows little or no increase.

In 14 patients after delivery the cell volume increased steadily so that at from twelve to fourteen days post partum it was normal—43 per cent. The loss of blood, up to 350 cc., did not visibly affect the cell volume. The behavior of the cell volume in these cases may be described as representing the entirely normal manner in which the physiologic proportion between blood cells and plasma is restored after pregnancy. Twenty patients, after delivery, showed a decrease in the hematocrit reading, which was lowest on the first to the third day (usually on the second). This dilution of the blood was, in nearly all cases, far greater than would correspond to a compensation for the blood lost, and it is to be conceived as probably representing a compensation, possibly an overcompensation, for a previous concentration of the blood (during labor). Of the 20 patients with low cell volumes, after twelve days 5 had hematocrit values over 40, while the remaining 15 showed values between 38 and 40. The increase in cell volume during the puerperium may be due to the new formation of erythrocytes or to the condensation of the blood. The rapidity with which the increase takes place speaks strongly in favor of the view that it is a condensation that occurs.

Peters and Van Slyke,¹¹ basing their opinion on the reports of others, stated that there is a slight increase in blood and plasma volumes in pregnancy and a reduction in hemoglobin, cell volume and erythrocytes, which is somewhat too large to be explained by the hydremia. They therefore concluded that there is apparently a diminution of the body's supply of hemoglobin.

In table 1 we have listed data collected from the literature on the different constituents mentioned. The ranges and averages of the dif-

10. Skajaa, K.: *Acta obst. et gynec. Scandinav.* 8:371, 1929.

11. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, vol. 1, 1931, and vol. 2, 1932.

TABLE 1.—Averages for Hemoglobin, Hematocrit and Erythrocyte Determinations in Pregnancy

Author	Year	Method	Hemoglobin, Gm.			Erythrocytes, Millions			Hematocrit, per Cent		
			Standard	Normal	Preg-nancy, Minimum Average	Normal	Minimum Average	Normal	Preg-nancy, Minimum Average	No. of Deter-minations	
Bernhard (München. med. Wchnschr. 39: 197, 1892)....	1892	Fleischel	15.8	12.6	12.6	4.56	4.55	
Thompson (Bull. Johns Hopkins Hosp. 15: 205, 1904)...	1904	Gowers	65%	4.30	
Gram (Ugesk. f. læger S2: 1609, 1920).....	1920	Autenrieth-St Venous blood	13.8	11.6	10-11	36-45	62	
Kerwin and Collins (Am. J. M. Sc. 172: 548, 1926).....	1926	Tallqvist	15.8	13.1	242	
Kühnel ⁴	1926	Sahli Venous blood	17.2	15.8	12.7	39.5-44.5 Citrate	15	
Moore (Am. J. Obst. & Gynec. 18: 424, 1929).....	1929	Dare	10.8	4.14	100	
Jerlov (Acta obst. et gynec. Scandinav. 8: 356, 1929)....	1929	Autenrieth-St	13.8	92	70%	1,143	
Galloway (J. A. M. A. 93: 1695, 1929).....	1929	Sahli	17.2	11.1	3.87	382	
Bland, First and Goldstein (Am. J. M. Sc. 179: 48, 1930)	1930	Dare	18.8	10.2	3.50	300	
Harvey (Am. J. Obst. & Gynec. 21: 476, 1931).....	1931	Sahli Venous blood	17.2	13.8	3.58	39.8	100	
Lyon (J. A. M. A. 92: 11, 1929).....	1929	Sahli	17.2	12.9	3.51	200	
Dietrich (Arch. f. Gynäk. 94: 383, 1911).....	1911	Sahli	17.2	12	Increase	4.50	Increase	19	
Skajaa ¹⁰	1929	Venous blood	43-47.5 44.4	27.5-44.5 36.4	120	
Plass and Bogert ⁹	1924	Venous blood	Oxalate	39.5	78	

[†] Standardized by the oxygen capacity method.

ferent constituents are as follows: hemoglobin, from 10.2 to 13.8 Gm., average 10.8 Gm., per hundred cubic centimeters of blood; erythrocytes, from 3,500,000 to 4,550,000, average 3,910,000, per cubic millimeter, and hematocrit reading, from 31.6 to 39.8 per cent, average 35.8 per cent. It is evident that there is a lack of uniformity in the results, owing, in part, to a failure to use proper methods or apparatus. For example, only two of the investigators standardized their hemoglobinometers with the oxygen capacity method. Another factor which causes confusion is the difference in the hemoglobin standard for the different methods. Apparently three of the investigators determined red cell counts in normal

TABLE 2.—*Averages for Hemoglobin, Hematocrit and Erythrocyte Determinations in Normal Women*

	Number of Women	Standardized Method	Hemoglobin, Gm. per 100 Cc. of Blood		Hematocrit, per Cent, Range Average	Erythrocytes, Millions, Range Average
			Standard = 100%	Range Average		
Bie and Moeller (Arch. d. mal. du cœur 15:177, 1922)	10	Colorimeter, oxygen	12.3-13.9 13.2 38.7	4.25-5.21 4.74
Gram and Norgaard (J. Biol. Chem. 56:429, 1923)	10	Colorimeter, oxygen	13.8	12.1-14.1 13.0	38.8-43 Hirudin 40.6	4.36-5.05 4.65
Williamson (Arch. Int. Med. 18:505, 1916)	49	Spectrophotometer	15.58
Haden ¹⁴	30	Van Slyke, oxygen	15.3*	13.34	41	4.38
Osgood and Haskins (Arch. Int. Med. 39:643, 1927; Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co., 1931)	100	Colorimeter, acid-hematin, oxygen	14.3*	12-15.5 13.7	37-45 41	4.30-5.30 4.80
Wintrobe ¹²	50	Newcomer, oxygen	14.2* 13.76	31-41.5 39.5	4.64-5.22 4.93
Average accurate methods	278	13.91	41.1	4.78

* Amount of hemoglobin per five million cells per hematocrit reading of 46 (Haden), 48 (Osgood and Haskins) and 42.8 (Wintrobe).

nonpregnant women as a control, and their results are therefore accurate relatively (the same error would occur in all determinations) but not absolutely, as would be the case if they had used a certified or standardized hematocytometer. Only four of the investigators determined the cell volume per hundred cubic centimeters or the hematocrit value, and yet it is the easiest and, at the same time, one of the most accurate determinations possible. Thus, it is evident that a study of the hemoglobin and hematocrit values and red blood cell count, together with determinations of blood volume, on the same women throughout pregnancy and the puerperium, with properly controlled methods, is necessary before positive statements can be made as to absolute changes in these substances.

In table 2 we have listed published data obtained with standardized methods on hemoglobin, hematocrit estimations and erythrocytes for normal nonpregnant women, together with a grand average calculated by

Wintrobe,¹² who was able to collect accurate data on only 260 women, and yet, with such a small group, we speak of a normal hemoglobin. The hematocrit values and red blood cell counts obtained by different investigators check very closely. So far as hematocrit determinations are concerned, the results are consistent, if one uses hirudin or heparin as an anticoagulant, but if one uses an electrolyte, such as citrate or oxalate, unless the solution is isotonic, one must correct for the shrinkage in cell volume (2 to 5 per cent), due to the hypertonicity of the salt. The maximum error in the hematocrit determinations is 2 per cent of the reading. The red cell counts, if made with a certified pipet and hematocytometer, have an error of 5 per cent. Likewise, the aver-

TABLE 3.—*Methods for Determination of Hemoglobin and Probable Errors*

		Volume of Blood	Probable Error, per Cent*	Standard, Gm. per 100 Cc. Blood
Williamson.....	Spectrophotometer, pure hemoglobin	Drop	1
Van Slyke.....	Oxygen capacity	1 to 2 cc.	0.5
Van Slyke.....	Carboxyhemoglobin	1 to 2 cc.	0.5
Haldane-Palmer.....	Colorimeter, carboxy- hemoglobin	0.1 to 0.5 cc.	1 to 2	13.8
Osgood and Haskins.....	Colorimeter, acid- hematin	1 cc.	1 to 2	13.8
Newcomer.....	Colorimeter, plate	0.02 cc.	5 to 40	16.9
Wintrobe.....	Colorimeter, plate	3 †
Sahli, original.....	Colorimeter	0.02 cc.	25 to 40	17.2
present.....	14.0
Dare, prior to 1926.....	Colorimeter	Drop	20 to 40	13.8
1931.....	Colorimeter	16.0
Tallqvist.....	Colorimeter, paper	Drop	20 to 40	15.8

* According to F. Schwentker.

† Newcomer plate with 19 per cent error; correction curve reduced error to 3 per cent.

age hemoglobin per hundred cubic centimeters of blood lies between certain narrow limits, but when one notes the various methods used to determine hemoglobin content (table 3) and the inherent errors of each, as determined by Schwentker,¹³ Wintrobe,¹² Haden,¹⁴ and others, one no longer wonders at the marked discrepancies in reports on hemoglobin determinations.

The standards of all methods for determining hemoglobin are based on the oxygen capacity, if the hemoglobin is normal. Many colorimetric methods will give exact results, but if the hemoglobin is abnormal (e. g., methemoglobin) high readings will be obtained with all methods, except with the oxygen capacity method. In a recent case report on

12. Wintrobe, M. M.: Blood of Normal Young Women Residing in a Sub-tropical Climate, Arch. Int. Med. 45:287 (Feb.) 1930.

13. Schwentker, F. F.: J. Lab. & Clin. Med. 15:247, 1929.

14. Haden, R. L.: Folia haemat. 31:113, 1925.

methemoglobinemia in pregnancy, one of us (W. J. D.)¹⁵ pointed out certain errors that can occur in determinations on patients with abnormal hemoglobin. Therefore, finding the oxygen capacity is the ideal method, but it requires fifteen minutes or longer for a single determination, and we believe, because of the daily variations which we have found to be as much as 10 to 15 per cent, that a large number of determinations with a fairly accurate procedure are of far greater value than a few with the highest degree of accuracy. Of the numerous methods with which hemoglobin can be accurately determined by a short colorimetric procedure, that of Palmer,¹⁶ in which it is determined as carbon monoxide hemoglobin, has been used by us since 1924, and it is noteworthy that Peters and Van Slyke,¹¹ in their monograph on biochemical methods, give precedence to this method above other colorimetric procedures. It has an error of less than 2 per cent. For purposes of comparison and for clearness, we are reporting our results in grams of hemoglobin per hundred cubic centimeters of blood. The figures for oxygen capacity can be obtained by multiplying the grams of hemoglobin by 1.34 (1 Gm. of hemoglobin theoretically combines with 1.34 cc. of oxygen).

METHOD

Studies were made on venous blood taken after at least a twenty minute period of rest, if the patient was ambulatory, without stasis, using heparin as an anti-coagulant (heparin does not affect the size or volume of cells). Erythrocyte counts were made with a Bureau of Standards certified pipet and hematocytometer. Hematocrit determinations were made in Plass hematocrit tubes and hemoglobin determinations were made with the Palmer carbon monoxide hemoglobin method, in a few of the early cases with 0.2 cc. of blood diluted to 20, and in the remainder with 0.5 cc. diluted to 50. All of the pipets were either certified or calibrated in the laboratory. The hemoglobin standards were made up fresh each week from a standard with a known oxygen capacity. The oxygen capacity of the blood of one of the patients was determined each week as an additional control of the standard. Determinations of blood and plasma volume, as described in the preceding report,¹⁷ were made in addition. The means for the total number of cases are based on all of the patients studied, for series A on the patients followed throughout pregnancy and the puerperium, and for series B, on those followed from late pregnancy to eight weeks post partum.

In table 4 are listed the variations and averages in hemoglobin per hundred cubic centimeters of blood for the entire series throughout pregnancy and the puerperium. For the first trimester the mean for the total cases was based on the patients whose hemoglobin was within the normal range, namely, from 11 to 16.5 Gm. All other means are

15. Dieckmann, W. J.: Methemoglobinemia in Pregnancy, *Arch. Int. Med.* **50**:574 (Oct.) 1932.

16. Palmer, W. W.: *J. Biol. Chem.* **33**:119, 1918.

17. Dieckmann, W. J., and Wegner, C. R.: The Blood in Normal Pregnancy: I. Blood and Plasma Volumes, *Arch. Int. Med.* **53**:71 (Jan.) 1934.

based on all of the estimations for hemoglobin, unless the patient had a hemorrhage or the findings were obviously abnormal. While these variations of the mean seem marked, mathematically, the difference between the various means for the different periods of pregnancy is insignificant. However, in series A and B, in which the same patients are followed, the changes are of significance. In series A the hemoglobin is slightly below normal (14.3 Gm. per hundred cubic centimeters of blood) at from ten to fifteen weeks' gestation; it decreases still more at from twenty-six to thirty-five weeks to a figure which is 15 per cent below normal; it increases slightly at term, decreases after delivery, and at two weeks post partum it is still 17 per cent

TABLE 4.—*Hemoglobin, Grams Per Hundred Cubic Centimeters of Blood: Variations and Averages in Pregnancy and the Puerperium*

Hemoglobin, Gm. per 100 Cc.	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
6.9-9.9.....	3	2	4	6	1
10.0-11.9.....	5	1	5	10	6	8	2
12.0-13.9.....	10	4	14	31	12	12	6
14.0-15.9.....	9	3	3	10	3	4	2
16.0-17.3.....	2	..	1	2	..	2	..
Total.....	26	8	26	55	25	32	11
	Mean						
Total cases.....	13.6 \pm 0.23	12.5 \pm 0.25	13.0 \pm 0.15	12.1 \pm 0.24	11.9 \pm 0.24	12.5 \pm 0.43
Standard deviation	1.73	1.86	1.62	1.80	2.00	2.10
Series A.....	13.80	12.20	12.40	11.78	
Series B.....	12.0	11.6	11.1	

below normal. In series B the hemoglobin at term is 15 per cent below normal, and at eight weeks post partum it is still 14 per cent below normal. Our data also show the wide range of hemoglobin in normal pregnant women and reveal that in some patients it may be from 30 to 50 per cent below the normal, without the occurrence of any symptoms or signs. The patients were all from the clinic; they were not selected, and yet only 5 had an initial hemoglobin content less than 11 Gm. (7.7, 7.8, 9.0, 9.3, 10.6). The initial hemoglobin content was normal in 6 patients, but decreased markedly during pregnancy, the minimum figures varying from 9 to 11 Gm. Seven patients had normal amounts of hemoglobin ante partum, but decreased amounts post partum, the figures varying from 7 to 11 Gm.

Dreyer and his co-workers¹⁸ and Rabinowitch¹⁹ have made hourly or bi-hourly determinations of the hemoglobin content of the blood of

18. Dreyer, G.; Bazett, H., and Pierce, H.: *Lancet* 2:588, 1920.

19. Rabinowitch, I. M.: *J. Lab. & Clin. Med.* 9:120, 1923.

adults throughout the day, and they agree in concluding that in a given subject the difference between the lowest and highest hemoglobin content observed during the same day may amount to from 20 to 30 per cent of the average content. Peters and Van Slyke stated that Mackay and Hiller have observed a fairly steady change in hemoglobin content during the day in the blood of laboratory workers, with differences as great as 1.5 Gm. of hemoglobin. They believe that variations of from 20 to 30 per cent appear to be rare in the resting or only moderately active person. Smith²⁰ stated that variations of hemoglobin and erythrocyte determinations are within the limit of error for hourly observations during an eight hour period, that food, rest or moderate activity causes no significant variations and that there may be real differences on different days or over a long period. Unpublished work of ours, in which we determined the oxygen capacity, carboxyhemoglobin and hematocrit value on seven persons, indicates that the hemoglobin may vary from 1 to 15 per cent during the forty-eight hour study, with the subject carrying on his usual work. Since Jan. 30, 1928, the hemoglobin content of one of us (W. J. D.) has been determined twenty-five times and, with but one exception, has ranged from 16 to 18.4 Gm., but the majority of the readings have been 17.5 ± 1 Gm. During the forty-eight hour study the hematocrit was remarkably constant, all readings checking within less than 3 per cent.

In table 5 are listed a series of hemoglobin, hematocrit and serum protein determinations during labor and the early puerperium. With the exception of patient 60, there were marked variations in hemoglobin, but there were changes of the same magnitude in hematocrit estimations, blood and plasma volumes and serum protein, thus indicating that the variations are due to concentration or dilution of the blood. It is evident that hemoglobin, hematocrit or erythrocyte determinations during labor or within twenty-four hours post partum are of comparatively little value in ascertaining whether or not the patient has normal blood. Keith,²¹ in wounded soldiers, found variations as great as 40 per cent in blood volume and in hemoglobin and hematocrit determinations within a period of a week, owing to replacement of volume with, primarily, water (plasma), but there was also a more rapid increase in cells than it would conceivably be possible to manufacture, suggesting that in conditions in which the blood volume fluctuates, the

20. Smith, C.: Normal Variations in Erythrocyte and Hemoglobin Values in Women, *Arch. Int. Med.* **47**:206 (Feb.) 1931.

21. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Haemorrhage, Medical Research Committee Special Report no. 27, London, His Majesty's Stationery Office, 1919.

TABLE 5.—*Variations in Hemoglobin, Hematocrit, Serum Protein and Blood Volume During Labor and the Puerperium*

Number, Gravidity, Color, Age	Date	Comment	Hemoglobin, Gm. per 100 Cc.	Hematocrit, per Cent	Blood Volume, Cc.	Plasma Volume, Cc.	Serum Protein, per Cent	Erythrocytes, Millions
60 I C*	5/12	Late in labor	12.5	38	4,822	2,990	6.7	4.38
		1.5 hrs. pp.†	11.5	36	100 cc. blood loss		6.1	
		6 hrs. pp.	11.0	36	5.6	
23	5/13	12 hrs. pp.	11.0	36	5,318	3,404	5.9	
		24 hrs. pp.	11.0	34	5.7	
	5/14	48 hrs. pp.	11.0	35	6.3	
	5/15	72 hrs. pp.	11.0	35	4,687	3,047	5.5	3.47
38 VI O	3/ 6	12.5	36	5,617	3,595	6.0	4.49
	3/10	14.5	40	6.6	
	3/17	Early in labor	15.3	41	6.6	
27		Late in labor	16.2	42	150 cc. blood loss		7.1	
		1 hr. pp.	15.7	41	6.6	
		6 hrs. pp.	13.8	42	6.4	
	3/18	12 hrs. pp.	13.4	40	5,176	3,106	6.2	3.79
		24 hrs. pp.	13.1	39	5.8	
	3/19	48 hrs. pp.	13.1	38	6.5	
	3/20	72 hrs. pp.	13.8	39	4,483	2,735	6.7	3.86
	4/ 8	24 days	12.5	36	3,975	2,544	6.3	4.14
58 I W	11/20	13.1	39	6,557	4,000	6.2	4.26
	11/25	Late in labor	11.5	39	100 cc. blood loss		6.4	
		1 hr. pp.	12.0	38	6.3	
20	11/26	6 hrs. pp.	9.2	30	5.7	
		12 hrs. pp.	10.6	5.1	
		24 hrs. pp.	13.1	37	6.0	
	11/28	60 hrs. pp.	12.0	36	6.1	
	11/29	84 hrs. pp.	11.5	34	4,545	3,000	6.2	3.93
	12/ 6	12.0	34	5,612	3,704	...	3.86
	1/28	8 wks.	14.5	40	6.9	
34 I O	12/18	14.5	40	6,000	3,600	6.6	4.50
	1/13	Early in labor	13.1	40	6.3	
	1/15	Late in labor	16.3	44	550 cc. blood loss		7.1	
25		1 hr. pp.	13.1	39	6.1	
		6 hrs. pp.	11.5	36	6.3	
	1/16	12 hrs. pp.	12.0	37	4,161	2,622	6.2	3.97
		24 hrs. pp.	11.0	34	5.8	
	1/17	48 hrs. pp.	12.0	34	5.4	
	1/19	82 hrs. pp.	11.0	32	6.0	
	1/20	5 days	11.5	33	3,876	2,597	5.9	4.06
	3/11	8 wks.	12.0	39	5,193	3,168	7.3	4.28

* C indicates colored race; W, white race.

† pp. indicates post partum.

TABLE 6.—*Hemoglobin in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and the Puerperium*

Hemoglobin, Gm. per Kg.	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
4.0-5.9.....	1	1	3	3	..
6.0-7.9.....	6	..	4	6	6	8	1
8.0-9.9.....	7	3	8	16	4	7	1
10.0-11.9.....	3	3	9	19	10	5	2
12.0-13.9.....	6	2	2	12	1	7	4
14.0-15.9.....	3	..	2	1	1
16.0-18.2.....	1	1	1	1
Total.....	26	8	26	54	25	32	11
	Mean						
Total cases.....	10.8 ± 0.42	10.0 ± 0.31	10.3 ± 0.18	9.1 ± 0.42	9.8 ± 0.38	
Standard deviation	3.14	2.36	2.02	3.10	3.18	
Series A.....	10.52	9.28	9.15	9.93	10.90	
Series B.....	9.82	8.7	7.9	9.53

body either holds or builds up a store of reserve cells in the spleen, liver, mesenteric capillaries, and other parts. Gross fallacies in the erythrocyte counts are particularly evident (patient 60).

In table 6 are listed the variations and averages of the grams of hemoglobin per kilogram of uncorrected body weight. The total amount of hemoglobin was obtained by multiplying the grams of hemoglobin per hundred cubic centimeters by the blood volume in cubic centimeters, divided by 100. The grams per kilogram were then obtained by dividing the total hemoglobin by the weight. The normal amount of hemoglobin per kilogram, according to the data of Rowntree and Brown,²² is 12 Gm. In pregnancy there are marked variations with a decided tendency toward low values. The means for the different periods of the total cases show no significant change. Series A shows a decrease in grams of hemoglobin per kilogram throughout pregnancy, reaching a minimum at term and returning to normal at from ten to fifteen days post partum. Series B shows an average which is lower than the general average at term, with a 20 per cent additional decrease at from ten to fifteen days, and a figure at eight weeks which is still a little below that of the figures for term. It would seem that as the weight (a considerable portion of which is actual maternal tissue requiring adequate blood supply) increases in pregnancy, the body attempts to maintain a constant amount of hemoglobin per kilogram, but after delivery this mechanism does not seem to function so well (lactation?), and at eight weeks post partum the amount of hemoglobin per kilogram is still decidedly below normal. It is also evident from the data that many parturient women go through pregnancy with very low amounts of hemoglobin per kilogram, but relatively normal amounts of hemoglobin per hundred cubic centimeters, and this deficiency may explain certain of the obscure cases of obstetric shock, infection and death.

In table 7 are listed the variations and averages for the hematocrit determinations in pregnancy and the puerperium. The majority of the figures are between 33 and 42 per cent, but the number of low cell volumes increases during pregnancy and especially post partum. There are no significant differences between the means of the total number of cases, but the changes in series A and B are of significance because the same patients were followed. In series A the average hematocrit value is 7 per cent below normal (43) in the first trimester, 14 per cent in the second and 11 per cent at term, and at two weeks post partum it is still 6 per cent below normal. The hematocrit value in series B at from ten to fifteen days is 16 per cent, and at eight weeks it is still 13 per cent below normal. Several explanations of this

22. Rowntree, L. G., and Brown, G. E.: *Volume of the Blood and Plasma*, Philadelphia, W. B. Saunders Company, 1929.

decrease in the hematocrit value are possible: (1) The cells decrease in size; (2) there is a greater increase in plasma than in blood volume, and (3) there is an actual decrease in the total number of cells. The individual cell volumes have been determined and found to be normal or even a little larger than normal. Our averages for changes in blood and plasma volume show that there is only a slightly greater increase in plasma than in blood, but a study of individual patients in table 9 indicates that the increase in plasma is usually greater than the increase in blood; therefore, the cell volume is diminished. Data for changes in total amount of erythrocyte mass prove that there is a definite increase,

TABLE 7.—*Percentage of Hematocrit: Variations and Averages in Pregnancy and the Puerperium*

Hematocrit, per Cent	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
22-27.....	1	..	2	2	..
28-32.....	3	5	3	4	1
33-37.....	7	2	9	14	10	7	2
38-42.....	14	6	12	33	8	14	8
43-47.....	5	1	..	3	2	4	..
48-52.....	1	1	..	1	..
Total.....	26	9	26	56	25	32	11
Mean							
Total cases.....	39.6 ± 0.44	36.9 ± 0.55	38.3 ± 0.35	36.0 ± 0.52	37.7 ± 0.66	38.2 ± 0.65
Standard deviation	3.35	4.18	3.93	3.88	5.53	3.22
Series A.....	39.8	36.9	38.1	38.0	40.1	
Series B.....	37.6	36.0	35.6	

but it is not equal to the increase in plasma; consequently the cell volume is relatively, but not actually, diminished.

In table 8 are listed the variations and averages of erythrocyte counts during pregnancy and the puerperium. The wide range, with the lower figures increasing in number toward term, is noteworthy, but the striking fact is the rapid return to normal post partum. The erythrocyte counts in the first trimester are normal, decrease during the period from the twenty-sixth to the thirty-fifth week, increase at term and decrease during the first post partum week, but are normal at three weeks post partum. The difference of the means for the first period and for the period of from twenty-six to thirty-five weeks is of significance. Series A and B show similar changes. Thus it is evident that the number of erythrocytes per cubic millimeter decreases in pregnancy, but that post partum the body is able to manufacture red blood cells but is not able to replace the hemoglobin as rapidly as the cells. The number of cells is relatively but not actually decreased. An expla-

nation similar to that given for variations in hematocrit readings explains this phenomenon. (The hematocrit value is measured as the cubic centimeters of cells per hundred cubic centimeters of blood, and the erythrocyte counts are measured as the number of cells per cubic millimeter. Thus the determinations are similar, but differ in the unit used.)

The changes in hemoglobin, hematocrit and erythrocyte determinations are even more evident in individual patients than in the group. It is impossible to list all of the data, but in table 9 are grouped normal patients (series A) in whom repeated determinations were made throughout pregnancy and the puerperium. The majority of the patients show a decrease in hemoglobin, hematocrit and erythrocyte determi-

TABLE 8.—*Erythrocytes, Millions per Cubic Millimeter: Variations and Averages in Pregnancy and the Puerperium*

Erythrocytes, Millions	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
3.0-3.4.....	2	2	6	5
3.5-3.9.....	2	1	16	10	8	5	2	..
4.0-4.4.....	15	5	5	28	10	12	4	6
4.5-4.9.....	4	3	..	12	1	4	4	4
5.0-5.4.....	4	..	1	1	..	2	..	1
Total.....	25	9	24	53	25	28	10	11
	Mean							
Total cases.....	4.45 ± 0.057	3.88 ± 0.05	4.25 ± 0.037	3.87 ± 0.06	4.12 ± 0.07	4.34	
Standard deviation....	0.425	0.386	0.40	0.413	0.56		
Series A.....	4.38	3.91	4.20	3.85	4.24		
Series B.....	4.23	3.98	4.34	4.44

nations during pregnancy, and an increase post partum. The amount of hemoglobin and cells per kilogram tends to remain fairly constant during pregnancy. Furthermore, the majority of the patients weigh more after pregnancy than they did before, and therefore require more blood. Likewise, many patients begin pregnancy with a subnormal hemoglobin content and cell volume, and although the total amount after delivery is greater than that found early in pregnancy, it is still below normal. In patients 1, 2, 3, 5, 12 and 13, especially, marked changes occurred during pregnancy and the puerperium and in patient 7 during the puerperium. Tables 9 and 10 demonstrate the fallacy of erythrocyte determinations, even with certified apparatus. That is, the cell count in pregnancy is no index of the amount of hemoglobin and may actually be misleading (patients 1, 3, 8, 12 and 53). Since the cell is only a vehicle for hemoglobin, more time and care should be devoted to determining the latter. In fact, unless the volume of the individual cell is in question, erythrocyte counts should be discarded completely.

TABLE 9.—Data on Patients Followed Throughout Pregnancy and the Puerperium
(Series A) *

Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight, Kg.	Hemoglobin				Volume Change		Hematocrit			Erythrocytes, Mil- lions per C. Mm.
			Gm. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	Blood, per Cent	Plasma, per Cent	Change, per Cent	Total Volume, Cc.	Per Cent	
1	2	3	4	5	6	7	8	9	10			
1	13 wks.	46.3	13.8	9.3	429	1,245	40	4.66
II	29 wks.	55.9	12.5	11.2	627	146	160	166	153	1,903	38	3.86
W†	40 wks.	59.5	10.2	10.2	605	141	190	206	161	2,075	35	4.00
20	12 days	50.4	11.4	12.5	633	105	93	90	99	2,042	37	4.31
2	14 wks.	77.9	11.9	7.0	545	1,650	36	4.28
I	30 wks.	81.0	10.6	6.5	527	97	108	115	96	1,584	32	3.39
W	40 wks.	80.9	9.1	5.6	452	83	109	119	90	1,490	30	3.45
23	12 days	73.6	11.0	7.0	512	113	93	86	109	1,625	35	4.05
3	15 wks.	53.0	16.3	16.0	850	2,245	43	4.47
I	30 wks.	61.1	14.5	15.2	930	109	123	125	120	2,693	42	3.79
W	40 wks.	63.5	10.6	9.1	577	68	104	116	89	2,004	37	3.90
23	12 days	53.0	17.3	18.2	968	168	103	91	123	2,464	44
4	14 wks.	92.2	15.3	8.9	823	2,362	44	5.26
VII	27 wks.	91.7	14.5	10.0	976	111	118	122	112	2,649	42	4.89
W	40 wks.	87.0	14.5	11.9	1,036	126	133	133	133	3,143	44
30	14 days	82.7	14.2	9.9	817	79	81	75	83	2,760	48	5.38
5†	12 wks.	53.6	14.5	10.0	534	1,546	42	4.52
II	28 wks.	59.5	12.4	9.3	552	103	121	129	109	1,690	38	4.14
W	39 wks.	60.0	11.4	9.2	552	103	131	140	119	1,832	38	4.28
25	14 days	52.5	9.7	10.9	573	104	123	123	123	2,254	38	3.94
6	14 wks.	45.9	11.4	8.6	393	1,237	36	4.06
I	27 wks.	54.8	12.5	10.1	554	141	129	125	137	1,690	38	3.90
W	40 wks.	63.5	12.5	10.0	634	161	148	141	160	1,935	39	5.02
19	11 days	56.0	15.3	13.7	768	121	99	94	106	2,106	42	4.59
7	14 wks.	107.2	13.1	7.0	754	2,302	40	3.76
VI	30 wks.	112.5	12.5	6.6	741	98	103	110	93	2,127	36	3.87
W	40 wks.	114.6	13.1	7.4	848	112	112	112	113	2,583	40	4.09
31	5 days	100.3	12.5	7.8	784	92	97	103	87	2,250	36	3.37
	13 days	100.4	12.5	9.8	983	116	121	127	112	2,900	37	3.07
8	14 wks.	92.9	13.5	9.6	889	2,325	35	4.13
III	28 wks.	103.5	13.1	8.0	822	92	95	92	100	2,319	37	3.76
C	40 wks.	108.9	13.1	8.5	924	104	106	100	117	2,749	39	4.45
30	11 days	100.0	9.5	5.1	514	56	77	85	63	1,726	32	4.00
9	14 wks.	50.0	11.5	9.1	455	1,468	37	3.99
I	29 wks.	58.8	12.0	9.8	576	126	121	127	111	1,632	34	3.58
C	40 wks.	60.0	12.0	10.4	625	137	131	129	135	1,977	38	4.08
21	3 days	55.8	12.5	11.0	615	99	94	94	94	1,867	38	4.00
	12 days	52.5	13.8	13.4	704	113	98	92	108	2,144	42	4.19
10	20 wks.	71.8	13.8	10.3	735	2,136	40	4.34
I	36 wks.	75.5	16.2	12.2	1,040	142	120	113	132	2,828	44	4.91
W	3 days	70.3	14.5	11.0	768	74	83	88	99	2,120	40	4.18
26												
11	15 wks.	67.2	14.1	12.2	822	2,390	41	4.23
I	28 wks.	73.8	11.4	8.9	660	80	99	102	94	2,247	39	4.42
W	39 wks.	76.5	12.0	9.1	692	84	99	102	94	2,247	39	4.52
22	12 days	68.1	13.8	12.4	842	122	106	94	125	2,809	46	4.43
12	9 wks.	61.3	14.9	12.7	776	2,137	41	5.33
I	27 wks.	80.0	8.2	6.9	552	71	130	133	125	2,681	31	3.73
C	40 wks.	86.3	12.2	6.9	595	77	94	102	83	1,764	36	4.08
28	11 days	75.6	11.0	7.2	546	92	101	98	107	1,885	38	4.41
13	11 wks.	68.1	15.3	13.9	946	2,590	42
VIII	29 wks.	75.4	11.4	9.2	692	73	93	106	86	2,237	37	3.65
C	40 wks.	71.5	11.0	8.6	613	65	90	99	77	1,999	36	3.64
37	11 days	65.6	13.8	12.0	786	128	102	92	120	2,388	42
22	16 wks.	55.7	13.8	12.4	690	2,000	40	4.09
II	28 wks.	64.3	13.1	9.1	585	85	89	95	80	1,605	36	3.82
W	40 wks.	67.5	12.5	39
24	12 days	60.8	13.1	9.5	577	99	99	93	110	1,762	41

* Loss of blood at delivery, unless excessive or measured, is assumed to be approximately 200 cc.

† In this table, W indicates white race; C, colored race.

‡ Patient 5 had a cesarean section.

In table 10 essential data on series B are given. All but 2 of the patients at eight weeks post partum had hemoglobin and hematocrit values equal to or exceeding those found at term, but still below normal. The red blood cell counts show marked increases, so that at from ten

TABLE 10.—*Data on Patients Followed From Term to Eight Weeks Post Partum (Series B)**

Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight, Kg.	Hemoglobin				Volume Change		Hematocrit			Erythrocytes, Mil- lions per C.Mm.
			Gm. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	Blood, per Cent	Plasma, per Cent	Change, per Cent	Total Volume, Cc.	Per Cent	
1	2	3	4	5	6	7	8	9	10			
31	39 wks.	67.0	12.3	11.8	790	2,557	39	4.62
I	12 days	56.5	13.8	10.8	610	77	67	64	73	1,855	42	5.06
C†	8 wks.	53.6	15.3	15.2	815	103	81	74	91	2,339	44	4.93
15												
32*	40 wks.	65.0	13.1	11.2	727	2,222	40	4.07
I	3 days	58.0	10.9	7.1	413	57	68	77	55	1,212	32	3.29
W	12 days	55.5	10.4	8.0	443	61	77	82	69	1,542	36	4.32
27	8 wks.	60.5	13.8	10.4	628	86	82	82	82	1,818	40	5.09
33	40 wks.	103.4	11.0	6.1	630	1,824	32	3.32
II	3 days	90.0	12.0	7.9	712	113	104	98	117	2,137	36	4.20
W	19 days	87.5	12.0	7.4	648	103	95	89	107	1,942	36	4.53
29	9 wks.	89.2	12.0	8.2	734	117	107	104	114	2,079	34	4.06
35*	36 wks.	63.1	11.4	8.6	582	1,932	38	4.31
I	11 days	61.5	10.6	7.1	434	75	80	88	68	1,308	32	4.03
W	8 wks.	53.6	11.6	8.5	496	85	84	84	84	1,626	38	4.48
24												
36	40 wks.	68.4	9.3	6.3	430	1,487	32	3.74
I	3 days	63.0	6.9	5.1	324	75	101	110	82	1,221	26	3.33
O	12 days	56.8	8.2	5.2	295	69	78	86	61	907	25	3.11
25	8 wks.	54.5	8.2	6.7	363	84	96	100	87	1,291	29	4.09
37	38 wks.	82.0	11.0	10.6	869	2,990	38	4.37
III	12 days	73.0	11.0	6.6	479	55	61	60	62	1,866	39	4.50
W	8 wks.	75.0	11.0	9.4	706	81	81	85	75	2,237	35	4.59
30												
39	39 wks.	62.5	14.0	11.6	785	2,356	42	4.49
I	11 days	51.9	12.6	9.8	455	58	64	67	61	1,445	40	4.39
W	17 wks.	50.0	13.8	6.4	438	56	57	59	54	1,272	40	4.57
17												
40	40 wks.	54.0	11.0	9.4	505	1,650	36	4.39
III	3 days	48.2	13.8	13.9	670	133	106	96	124	2,044	42	4.56
C	25 days	46.8	13.1	12.8	600	119	100	100	99	1,635	36	4.44
28	8 wks.	47.2	12.6	10.4	490	97	85	82	89	1,475	38	4.12
43	38 wks.	72.2	12.6	10.6	765	2,372	39	4.51
I	5 days	63.5	14.5	11.2	707	92	80	71	95	2,242	46	4.44
C	19 days	62.2	13.8	15.6	970	127	115	110	124	2,953	42	4.79
17	8 wks.	61.9	12.6	10.4	695	91	84	86	82	1,945	38	4.13

* Patients 32 and 35 had losses of blood amounting to 1,020 cc. and 400 cc. \pm , respectively; the other patients had losses of from 50 to 200 cc. \pm .

† In this table, W indicates white race; C, colored race.

to fifteen days they were normal, indicating that the hematopoietic tissue was able to form erythrocytes but not to give them their normal amount of hemoglobin. Patient 32 had a measured blood loss of 1,020 cc., which was reflected in a 32 per cent decrease in blood volume and a 43 per cent decrease in total hemoglobin, but only a 17 per cent decrease

in grams of hemoglobin per hundred cubic centimeters of blood. The recovery was extremely rapid, and at eight weeks the hemoglobin was essentially normal when calculated on the basis of both volume and weight. Patient 36 was first seen at term with a definite anemia, which

TABLE 11.—*Average Changes in Hemoglobin and Total Cell Mass Calculated from Variations in Total Amount, Using the Initial Determination As 100 Per Cent for the Antepartum Period*

	Hemoglobin		Cell Mass	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 26 to 35 weeks of gestation:				
Average increase for all patients	17	5.8	17	10.4
Average increase for those showing increase.....	7	33.0	9	27.1
Average decrease for those showing decrease.....	6	21.4	5	13.0
No change	4	0	3	0
From 36 to 40 weeks of gestation:				
Average increase for all patients	14	13.0	14	19.9
Average increase for those showing increase.....	7	42.7	9	38.4
Average decrease for those showing decrease.....	5	24.6	5	13.4
No change	2	0	..	0

TABLE 12.—*Average Changes in Hemoglobin and Total Cell Mass Calculated from Variations in Total Amount, Using the Last Antepartum Determination As 100 Per Cent for the Post Partum Period*

	Hemoglobin		Cell Mass	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 2 to 6 days post partum:				
Average decrease for all patients	24	17.3	24	15.2
Average decrease for those showing decrease.....	18	26.8	16	26.6
Average increase for those showing increase.....	3	23.0	3	22.3
No change	3	0	5	0
From 10 to 25 days post partum:				
Average decrease for all patients	40	8.3	40	10.5
Average decrease for those showing decrease.....	25	25.4	23	27.1
Average increase for those showing increase.....	11	26.4	13	15.7
No change	4	0	4	0
From 8 to 17 weeks post partum:				
Average decrease for all patients	10	12.8	10	15.8
Average decrease for those showing decrease.....	7	20.8	9	19.2
Average increase for those showing increase.....	1	17.0	1	14.0
No change	2	0	..	0

became more marked after delivery and at eight weeks post partum; the hemoglobin was 9.2 Gm. (59 per cent of the normal content). The hemoglobin per kilogram was also extremely low. As a rule, the hemoglobin for each person seems to be a rather fixed quantity with variation between narrow limits. With one exception, the hemoglobin of all of these patients in a period of eight weeks varied less than 10 per cent.

In tables 11 and 12 are listed the changes in hemoglobin and hematocrit values calculated on the basis of total amount. The method used in calculating the total hemoglobin has been described in an earlier

paragraph. The total amount of erythrocytes (leukocytes and platelets are included, but form only a small part of the total) is determined either by multiplying the cells per hundred cubic centimeters by the blood volume in cubic centimeters, divided by 100, or by subtracting the plasma in cubic centimeters from the blood volume. All antepartum values are divided by the first one obtained and the quotient multiplied by 100; thus all data are converted to a common basis, and changes in different patients can then be compared. Postpartum values were converted similarly, but the determination at term was used as the divisor. In other words, the first antepartum determination is assumed to be 100 per cent, and subsequent ones are expressed in percentage of increase or decrease relative to it. Similarly, postpartum determinations are expressed in percentage of decrease or increase, relative to the determination at term, which is assumed to be 100 per cent. Ante partum the cell mass increases proportionally more than the hemoglobin, but post partum both decrease by approximately the same amount. The antepartum increases occur early and are of considerable magnitude by the end of the second trimester, but reach their maximum at term. The average increase in cells at term is 20 per cent, and in hemoglobin, 13 per cent. The increase in hemoglobin and in cell volume is less than the increase in blood and plasma volumes. Therefore, there is a decrease in both of the former, and the statement made by Williams⁷ that the hemoglobin and cell volume are relatively, but not actually, diminished is confirmed.

Variations in hemoglobin, especially increases occurring within a period of one or two weeks, are difficult to explain. We do not believe that such a marked increase occurred, but we do believe that there is a measurable increase. The total figures are based on three separate determinations, each with an appreciable error; however, all determinations were made with the same conditions and by the same persons, and therefore the figures are significant.

Changes in volume of some of the abdominal organs will materially alter the blood volume. Barcroft²³ has demonstrated in the dog that the spleen shrinks markedly during pregnancy. This squeezing out of erythrocytes with a hematocrit value undoubtedly much higher than that of the blood would explain some of the rapid changes in the blood. Furthermore, the liver is also a reservoir for blood, and because of its size, changes in volume would affect the hematocrit and hemoglobin even more than changes in the spleen. Additional evidence of marked changes in hemoglobin is found in new-born babies in whom in the first week there is a reduction of the hemoglobin of from 20 to 30 per cent or more. This is demonstrated clinically by the varying degrees of icterus and decreases in hemoglobin.

23. Barcroft, J.: *Am. J. M. Sc.* **179**:1, 1930.

COMMENT

In the first article of this series we¹⁷ advanced the theory that the increase in blood and plasma volumes is necessary in part to supply the increase in maternal tissue, but that the major portion is required to permit proper gaseous metabolism on the part of the fetus. In this contribution we have demonstrated that the cell volume and amount of hemoglobin per hundred cubic centimeters of blood are decreased, but that the total amount of each is increased. There is no decrease in the size of the erythrocytes. There is also a decrease in serum protein and total electrolyte per hundred cubic centimeters of serum. Thus, there is a decrease in all factors concerned in maintaining the viscosity of the blood, which, of course, is also lowered, thereby probably decreasing the amount of work done by the heart without interfering with cell metabolism. While we have no plethysmographic data to confirm our theory, we believe that, owing to the absolute increase in blood volume and total hemoglobin, the increase in cardiac output and the decrease in viscosity, the volume of blood per minute supplying an organ is normal. Considerable support is given to this belief by the evident "well-being" experienced by the pregnant woman. It is a well known fact that the metabolism becomes more efficient during pregnancy, that weight is gained and retained after delivery and that, as a rule, multiparity does not preclude longevity, all of which would be impossible if pregnancy were habitually accompanied by tissue anoxemia.

CONCLUSIONS

Previously reported hemoglobin, hematocrit and erythrocyte values in pregnancy are, in many instances, at variance with each other, and the results are inconclusive because, with but few exceptions, the determinations were made with methods and apparatus which were not standardized, and they were not made on the same women throughout pregnancy. They are of value only in that they indicate the direction of the change.

Determinations of these constituents and of the blood volume were made on various groups of women for the different periods of pregnancy. While the means show a decrease in each substance, reaching a minimum in the last ten weeks, calculation of the difference between the means demonstrates that the change is of no significance.

Similar studies in which the same women were followed throughout pregnancy and the puerperium indicate that the following changes occur in the blood:

1. There is a definite decrease in the hemoglobin per hundred cubic centimeters of blood. The maximum decrease, amounting to 15 per cent, is from the twenty-sixth to the thirty-fifth week. At two weeks post

partum the hemoglobin is 17 per cent, and at eight weeks it is 14 per cent, below normal.

2. There is a slight but definite decrease in the hemoglobin per kilogram during pregnancy, and a more marked one after delivery. Apparently there is an attempt during pregnancy to compensate for the increase in tissue by increasing the hemoglobin, but post partum the stimulus is gone and there is a lag in the production of hemoglobin.

3. The changes in the hematocrit value are similar to those in the hemoglobin content. The maximum decrease during pregnancy is 14 per cent. The recovery after delivery is more rapid, although at eight weeks post partum the hematocrit value is still below normal.

4. The changes in the erythrocytes are also similar, but the count is normal at three weeks post partum, thus demonstrating the ability of the hematopoietic tissue to produce red cells, but its inability to stock them with the normal amount of hemoglobin.

5. The total amount of hemoglobin shows an average increase of 13 per cent, but individual cases show a marked gain during pregnancy and a retention of much of the gain post partum.

6. The total cell volume shows an average increase of 20 per cent, which is even greater in many individual cases, and a retention of many of the cells post partum.

7. The increase in plasma volume is definitely greater than the increases in cell volume and hemoglobin. Therefore, these constituents show a relative decrease and an absolute increase.

8. Since the erythrocyte is only a vehicle for transporting hemoglobin and since cell counts in pregnancy are often misleading, more time and care should be devoted to hemoglobin determinations.

9. In pregnancy a hemoglobin content under 10 Gm. per hundred cubic centimeters of blood should be diagnostic of anemia.

10. The changes in blood volume, cell volume and hemoglobin are a part of the mechanism by which the body is able to take care of its own increase in tissue and the metabolism of the fetus, with the expenditure of the least amount of work.

OSTEITIS DEFORMANS

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WITH A ROENTGENOLOGIC SECTION BY G. E. VILVANDRÉ

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Czerny,¹ in 1873, first used the term "osteitis deformans" to describe softening and deformity of the tibia and fibula in a young soldier. Paget,² however, was unaware of this when he published his classic description in 1877 and suggested the term "osteitis deformans" because of his belief in the inflammatory nature of the lesion. Since that time, Roberts and Cohen³ stated, more than three hundred cases of the disease have been described. In view of the fact that within four years we have observed thirty-four cases, it would appear that the disease is much commoner than was hitherto supposed. The increasing use of roentgenography is probably the explanation.

The present investigation, originally commenced in 1926 as an effort to ascertain the frequency of neurologic changes in osteitis deformans, expanded into a more comprehensive clinical and biochemical investigation.

REPORT OF CASES

CASE 1.—*History*.—F. N., a woman, aged 57, had complained of vague pains in her legs for twenty years. Seventeen years before examination the left shin-bone became prominent, and five years later both legs appeared to be bent, so that she had great difficulty in walking. For ten years she had been unable to walk, and she complained of vague aches like neuritis all over the body; these were worse in winter. For five years the head had been getting larger. During the last few months, her eyesight had become very poor, and straight lines appeared wavy in both the horizontal and the vertical direction. Six years before examination, hematemesis, thought to be due to gastric ulcer, occurred, and five years later, further hematemesis. Three children were alive and well. The patient showed a characteristic large head, with frontal bossing; marked kyphosis, lordosis and scoliosis; a diamond-shaped abdomen with a wide costal angle; exaggerated outward and forward bowing of the femora, tibiae and fibulae, which were bent to such an enormous extent as to cause crossing of the legs in scissor-like fashion;

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1. Czerny, V.: *Wien. med. Wchnschr.* **23**:896, 1873.

2. Paget, J.: *Tr. Roy. Med.-Chir. Soc.* **60**:37, 1877; **65**:225, 1882.

3. Roberts, R. E., and Cohen, M. J.: *Proc. Roy. Soc. Med.* **19**:13, 1926.

the humeri were bent forward and outward, and the ulnae were bent to give decubitus valgus. Examination of the cardiovascular system showed: blood pressure, 160 systolic and 80 diastolic; slight cardiac hypertrophy; the apex beat in the fifth space just external to the midclavicular line; an accentuated aortic second sound; systolic murmurs at the base of the heart and in the mitral area; slight thickening of the radial and brachial arteries, and tortuous temporal arteries. Crepitations were heard at the bases of both lungs. The liver was slightly enlarged. In the central nervous system no abnormalities were detected. Examination of the fundi revealed bilateral subretinal hemorrhages deep to the retinal vessels, macular hemorrhages in the nerve fibers, edema and pallor of the retina and vision of 6/60. Slight albuminuria was present. The Wassermann reaction was negative. No calcified vessels were seen on roentgenoscopic examination. The blood count showed: hemoglobin, 75 per cent; red cells, 4,350,000; leukocytes, 12,400; color index, 0.86; a differential cell count of 60 per cent neutrophils, 32 per cent small lymphocytes, 4.5 per cent eosinophils and 3.5 per cent large hyaline cells.

CASE 2.—*History*.—M. W., a woman, aged 44, during convalescence after removal of a multilocular ovarian cyst six years before examination, had a spontaneous pathologic fracture of the left femur on attempting to fasten her boot-lace. Roentgenography showed the fracture to be in the middle third of the femur, and the bone to be widened throughout its length, with much rarefaction and areas of compact bone. On failure to secure healing by splinting, the bone was plated; at operation it was found to be very soft. On clinical examination at that time no changes were observed in the other bones, but roentgenographic examination of the skull showed a porous thick vault with sagging of the posterior fossa. The roentgenologic diagnosis was osteitis deformans. For ten years the patient had had aching pains across the top of the head and down the back of the neck, occasionally in the frontal region and sometimes associated with vomiting. The headaches occurred every few days and lasted from a few minutes to a few hours. Speech was slow and sometimes difficult. For one year before the fracture the patient noticed creepy feelings in both legs when at rest, as though the muscles were twitching. She stated that she had to get up and work the legs about. For seven years she had had urgency of micturition, and during the past year also frequency, three times at night and six times during the day. For six and a half years, she had suffered from noises in the ears like rushing water. During the past year there had been increasing weakness and almost complete inability to walk. In the last three months diplopia had occurred. The past history was not significant. The patient had six children, aged 24, 22, 20, 15, 12 and 4. Examination revealed marked bulging of both temporofrontal regions of the skull, antero-lateral bowing of both femora and anterior bowing of both humeri; the rest of the skeleton was normal. Examination of the central nervous system showed slightly irregular pupils; bilateral wasting of the lower part of the trapezius muscle on both sides, with some winging of the scapulae; moderate wasting of the left calf, and a Babinski plantar response on the right side. Examination of the cardiovascular system showed a blood pressure of 135 systolic and 80 diastolic. There were slight thickening and tortuosity of the radial and brachial arteries, with visible pulsation. No gross cardiac hypertrophy was present. The eyes showed blue sclerae, nystagmus to the left, diplopia on the left side and unsustained nystagmoid movements to the right. The visual fields were normal; the disks were pale, with indefinite edges, and there was no papilledema. Otosclerosis was present in both ears. Roentgenography showed osteitis deformans of the skull,

vertebrae and femora. The spine showed marked flattening and compression of the lumbar vertebrae; the humeri gave a roentgenographic picture more in keeping with osteitis fibrosa than with Paget's disease.

CASE 3.—A. R., a man, aged 40, had noticed two years before examination the beginning of throbbing pain, which started in the occipital region and spread forward toward the ears. The pains were continuous but were worse at night. There was also a feeling of heaviness across the forehead. Eighteen months before examination he had three attacks of partial syncope in which he almost lost consciousness but did not fall down. Examination revealed marked forward and slight outward bending of both tibiae and outward and forward bending of both femora, with bowed legs. There were no obvious changes in the skull. Examination of the cardiovascular system showed: marked tortuosity, thickening and visible pulsation of the radial, brachial and temporal arteries, with Corrigan's pulse; capillary pulsation; the apex beat in the fifth space of the midclavicular line; an accentuated aortic second sound; a faint diastolic murmur to the left of the sternum, and a systolic murmur in the mitral area. The blood pressure was 180 systolic and 0 diastolic; aortic incompetence was probably present. There were crepitations at the base of the left lung. On examination the central nervous system showed: bilateral partial ptosis; Argyll Robertson pupils, with the right greater than the left; some cutaneous analgesia on the outer aspect of the upper part of the right arm and of the left forearm; some reduction in the sense of deep pain in the calf, and absence of the ankle jerk on the right side. The optic disks were pale. There was deafness of the right and left middle ear. Roentgenographic examination showed a cotton-wool appearance of the tibiae and fibulae, typical of Paget's disease. The Wassermann reaction was positive for the blood and the cerebrospinal fluid. The latter was macroscopically clear but contained 114 white cells per cubic centimeter, 90 per cent small lymphocytes and 0.03 per cent protein. Meningovascular syphilis was undoubtedly present in this case, but roentgenographic examination and estimation of the phosphatase content of the blood plasma indicated coexisting osteitis deformans.

CASE 4.—C. G., a man, aged 62, sustained a fracture of the neck of the left femur eight years before examination, following a severe fall. Union had taken place with external splinting. Eighteen months before examination, fracture of the neck of the right femur occurred following a fall. Examination revealed the following: marked forward and outward curving of both femora, especially the right, with bowing of the legs and separation of the internal condyles by 3 inches (7.6 cm.); gross thickening of the left clavicle, and a diamond-shaped abdomen with a wide costal angle. There were no obvious changes in the skull or spine. The findings on examination of the cardiovascular system were marked thickening and tortuosity of the brachial arteries, with visible pulsation, the tortuosity being excessive and snakelike. The radial arteries were apparently not affected. The blood pressure was 140 systolic and 90 diastolic; the apex beat occurred in the fifth space of the midclavicular line. Auricular fibrillation was present. No changes were found on examination of the central nervous system. There was gross pyorrhea. Roentgenographic examination of the left femur and pelvis showed osteitis deformans.

CASE 5.—W. L., a man, aged 50, had noticed that his vision was beginning to fail eighteen years before examination. Objects appeared dim, and reading became difficult. For twelve years this state of vision remained unchanged. Fourteen years before examination transitory paresis of both legs occurred. For ten years

there had been indefinite mental trouble, with several attempts at homicide and attacks of loss of memory. Shortly before examination he noticed deafness in the right ear and giddiness on rapid change of position. For five years he had had attacks of diplopia. He was addicted to alcohol. In 1910 the patient was seen by Foster Moore, who reported partial optic atrophy caused by anemia resulting from bleeding piles. The patient had suffered from the latter condition for ten years. The blood count at that time showed 40 per cent hemoglobin and 3,900,000 red cells. On Aug. 17, 1910, the piles were ligated. On October 27 the hemoglobin was said to be 100 per cent. The eyes were examined in 1918, and no appreciable change was observed. Examination revealed no gross changes in the skull or in any of the skeletal structures. Examination of the central nervous system showed that the pupils were equal but irregular, with poor reaction to light; they reacted well on convergence. The ocular movements were full, and there was no ptosis, squint or nystagmus. A slight relative nasal analgesia was evident; the facial movements were good and equal. The tongue protruded in the midline, and the palate moved symmetrically on phonation. There was no weakness, ataxia, wasting or dystonia. Hearing was diminished in both ears. The reflexes of the arm were normal. The abdominal reflexes were present and were equal; the knee jerks were present, although they were slightly diminished. The ankle jerks were obtained with difficulty. The plantar reflexes and postural sensibility were normal. There was relative thoracic analgesia from the second to the sixth dorsal segment. Examination of the cardiovascular system showed a blood pressure of 210 systolic and 110 diastolic. The radial and brachial arteries were thickened and slightly tortuous; no cardiac hypertrophy was detected. On examination of the eyes, fingers were seen at 1 foot (30.5 cm.) by the right eye and at 2 feet (61.2 cm.) by the left; the media were clear in both eyes. Both disks were pale, with cleancut edges; the physiologic cup showed the lamina cribrosa. There was no retinitis and no exudate along the vessels. Bilateral primary optic atrophy was found. The visual fields were not contracted. Irregular central scotoma was found in both fields. On roentgenographic examination no enlargement of the pituitary fossa was apparent; the clinoid processes could be plainly seen. There was no erosion, and the general view of the skull strongly suggested Paget's disease: the skull was thick; in places there was loss of differentiation between the inner and outer tables (thickened diploe); the bones were bottled, suggesting areas of thickening and rarefaction side by side. No abnormalities were seen in the tibiae. Dr. Vilvandré expressed the opinion that the changes in the skull were characteristic of Paget's disease. The Wassermann reaction was negative for the blood and the cerebrospinal fluid. Spinal puncture yielded 6 cc. of clear, colorless fluid in which no cells were found. The normal protein was 0.17. The urine was normal. A blood count showed: red cells, 4,500,000; hemoglobin, 75 per cent; color index, 0.83, and leukocytes, 7,800.

CASE 6.—A. L. B., a woman, aged 49, had suffered for seven years from lumbago, and for six years from pains in the knees, elbows and shoulders. For three years she had been unable to walk and was bedridden. Two years before examination the small joints of the hands were affected, becoming stiff and swollen. For seven years she had had amenorrhea, and two years before examination her teeth were extracted because of pyorrhea. She was married and had four children, the youngest of whom was 21 years of age. Examination revealed partial fixation of all the joints, with limited painful movements; glossy skin; ulnar deviation of the hands; lordosis, scoliosis and fixity of the spine. There was a slight outward bending of the femora. The costal angle was wide. No obvious changes

were found in the skull. Examination of the cardiovascular system showed a blood pressure of 210 systolic and 120 diastolic; the arteries were not grossly thickened. The apex beat was not located; there was a systolic murmur in the mitral area. The central nervous system was apparently normal. Roentgenography showed changes in both femora suggestive of osteitis deformans. Although the clinical picture suggested the diagnosis of rheumatoid arthritis, the roentgenograms and the high phosphatase content of the blood plasma indicated coexisting osteitis deformans.

CASE 7.—S. B., a woman, aged 68, had suffered from vague malaise for many years. She gave an indefinite history of paresis of the right arm several years before examination, followed by gradual recovery. Six weeks before examination, pain occurred in the left foot, with bluish discoloration, and there was some frequency of urination. Examination showed a thin old woman with marked bulging of the right parietal bone and enlargement of the head, the enlargement being limited, however, to the right side. The right femur was markedly bent in an outward direction, and the right tibia was bent forward and outward. The right ulna had a marked convexity in an outward direction, the arm being held in the pronate position. In contrast, the left arm and leg were apparently normal. The abdomen was diamond-shaped, with a wide subcostal angle. Examination of the cardiovascular system revealed a blood pressure of 200 systolic and 100 diastolic but with pulsations faintly heard down to 0. The blood pressure of the leg below the knee was 280 systolic and 160 diastolic. Cardiac hypertrophy was present. The apex beat occurred 1 inch (2.54 cm.) external to the midclavicular line; accentuated aortic second sounds with systolic murmurs were located at the base of the heart and in the mitral area. No aortic diastolic murmur was heard at the time of examination. All the vessels of the right leg were patent. On the left side the popliteal artery pulsated, but the posterior tibial artery and the dorsalis pedis were closed. Oscillometry showed absence of pulsation at the left ankle. The brachial and radial arteries were thick and tortuous, with visible pulsation and a collapsing pulse; the temporal arteries were thickened and tortuous. Roentgenography showed changes of osteitis deformans in the right femur. (In this case, as in several other cases, roentgenographic examination was limited to one or two bones for economic and other reasons.) The Wassermann reaction was negative. A few months after the patient was seen, sarcoma of the right femur developed.

CASE 8.—A. S., a woman, aged 49, had symptoms which had begun with pains in the head and right leg ten years previous to examination. The headache was of dull character and was especially noticeable in the right temporal region. For three years the patient had been getting deaf. During the last few years there had been dull, aching pains in the arms and legs. One year the right foot had twitched involuntarily. The patient had felt sleepy, and the lid of the right eye had tended to droop. During this period the head had been increasing in size. For six months there had been pain in the right shoulder as though a needle was being thrust there. There had also been some incontinence of urine and frequency of micturition. Examination showed gross enlargement of the skull, which was of enormous breadth, and marked bulging of the temporal and frontal regions, with apparently sunken orbital fossas. There were slight scoliosis and slight thickening of the upper end of the left tibia. Otherwise, there were no gross skeletal changes. On examination of the cardiovascular system the fundi showed arteriosclerosis of the retinal vessels. The blood pressure was 180 systolic and 100 diastolic. There were slight cardiac hypertrophy, the apex beat being in the fifth space of

the midclavicular line, an accentuated aortic second sound, and some thickening of the radial and brachial arteries, with marked tortuosity and thickening of both temporal arteries. No abnormalities were found in the lungs. There was deafness of the right middle ear. In the central nervous system all the reflexes were increased in the lower limbs, but the plantar reflex was normal. Roentgenography revealed osteitis deformans. The Wassermann reaction was negative.

CASE 9.—R. T., a woman, aged 54, had a history of aching pains in the legs, thighs and right arm of eleven years' duration. The legs gradually became bent, and five years before examination tended to cross one another in walking. The patient began to stoop and experienced some pain in the lumbosacral region. Three years before examination the pain spread upward and involved the whole spine and the back of the head. The pain was much worse when the patient stood still; she was unable to maintain an erect position for more than a few minutes, but was, nevertheless, able to walk. The head was becoming larger, and there was a dull ache in the left parietal region, which was usually likened to a nagging toothache, with acute exacerbations. There was some pain in the left foot. The patient was examined in 1925. The records stated that she had a broad, square forehead, thickening and outward bowing of the right humerus, anterolateral bowing of both femora and thickening and slight curving of both tibiae, which was greater on the right than on the left. No gross abnormalities of the spine were found, but there was a slight decrease in the lumbar curvature. At that time Robert Milne performed an osteotomy on the right femur. Microscopic examination showed osteitis deformans of the cortex of the femur. The bone was composed of numerous lamellar systems and was permeated by medullary spaces and widened haversian canals; these were occupied by delicate fibrous marrow. Toward one surface there was active resorption and deposition. The Wassermann reaction was negative. Examination disclosed: a very broad head with protuberant supra-orbital ridges, which were greater on the right than on the left; definite enlargement of both clavicles, which was more pronounced on the right than on the left; marked lordosis and kyphosis; a wide costal angle with a sulcus on the wall of the chest, and marked bowing of both femora and both tibiae. Examination of the cardiovascular system revealed a blood pressure of 165 systolic and 80 diastolic. Gross cardiac hypertrophy was found. There was accentuation of the aortic second sound; the apex beat occurred in the fifth space, $\frac{3}{4}$ inch (1.9 cm.) external to the midclavicular line. Marked thickening and tortuosities and visible pulsation of the radial, brachial and temporal arteries were present. The lungs and the central nervous system were normal.

CASE 10.—H. A., a man, aged 60, had noted bending of the left tibia for thirty years, and bending of the right tibia for almost as long. A few months after the onset of this trouble his head had begun to grow larger, so that while he had formerly worn a size $6\frac{7}{8}$ hat, he gradually came to need a $7\frac{3}{4}$. Practically coincident with the change in the shape of the leg he noticed shooting pains of knifelike character up and down the long axis of the leg. These occurred in attacks at intervals of a few weeks. They lasted only a few minutes but left a sensation of soreness which persisted for several hours or longer. If the pains came on while the patient was walking they were sufficiently severe to force him to stop, but they did not have the character of claudication. There was, however, no pain in the head until three years before the patient was examined, when shooting pains began in the temporal or occipital region, lasting a variable time. At first they occurred every few weeks, but at the time of examination they occurred every day and several times a day. Owing to progressive bending of

the lower limbs, the patient had been unable to walk for ten years. For many years he had suffered from chronic bronchitis. Examination showed a skull characteristic of Paget's disease, with marked bulging of the frontal, parietal and occipital bones, and bowing of both humeri, which was greater on the left than on the right, with decubitus valgus. The clavicles were thick and prominent; the costal angle was wide, and splaying of the ribs, gross kyphosis and lordosis were apparent. There was enormous forward and outward bowing of the femora and tibiae, that of the tibiae being so excessive that the legs were crossed in scissor fashion. Examination of the cardiovascular system showed marked thickening and tortuosity of the radial, brachial and temporal arteries. The blood pressure, however, was not high (135 systolic and 76 diastolic), and there was no gross cardiac hypertrophy. Scattered rhonchi could be heard throughout the lungs. There were no changes in the central nervous system. The Wassermann reaction was negative. The fundi showed choroiditis with secondary optic atrophy (Jeremy).

CASE 11.—E. L., a woman, aged 70, had suffered from delusional insanity while in the infirmary, where she was examined by one of us. It was impossible to obtain any definite history from the relatives. On examination the head was found to show the characteristic changes of Paget's disease; there was marked bulging of the right frontal and occipital regions. The clavicles were slightly enlarged, and there was well marked kyphosis. The costal angle was not widened, and no gross changes were observed in any of the limbs except some outward and forward bending of the left tibia. Marked cardiovascular hypertrophy, with thickening of the radial and brachial arteries and tortuosity of the temporal vessels, was apparent. The blood pressure was 160 systolic and 80 diastolic; the apex beat was in the fifth space $\frac{1}{2}$ inch (1.27 cm.) external to the midclavicular line; accentuation of the aortic second sound was detected. During examination of the central nervous system the patient gave no evidence of any delusions which the sister in charge stated had occurred at varying periods. However, she exhibited a very sluggish mentality, and it was practically impossible to obtain any response to questions. The pupils were irregular, the left being slightly greater than the right. Reaction to light and in accommodation was present. There was some keratitis of the right eye, with diffuse corneal opacity. The fundi, however, appeared to be normal. All the reflexes were elicited and were equal on both sides. There appeared to be loss of postural sensibility and vibratory sense in the left leg, and incomplete loss on the right. On roentgenographic examination the left tibia and the skull showed changes typical of osteitis deformans. Roentgenographs of the femora and of the right tibia, radius and ulna showed no abnormalities. The Wassermann reaction was positive.

CASE 12.—S. G., a woman, aged 65, had been confined to the infirmary for six years. Four years before examination she fractured her left femur; since that time she had been confined to bed. She complained of very severe headache but was unable to describe it. During the six months before examination she had three attacks of convulsions, with loss of consciousness. These were not accompanied by incontinence of urine or biting of the tongue. There was generalized twitching during the attacks but no evidence of focal spread. During the last attack she had repeated convulsions (status epilepticus); the attack had lasted four hours and had been followed by a comatose state of forty-eight hours' duration. Examination showed gross enlargement of the skull characteristic of osteitis deformans, with marked bulging of both the temporal and the frontal regions. The clavicles were grossly thickened. No obvious change was found in the upper limbs except definite tenderness at the lower end of the right humerus (spon-

taneous fracture?). The costal angle was very obtuse, with outward splaying of the ribs. The abdomen was diamond-shaped, and the pelvis was wide. There were moderate kyphosis, gross outward bending of the femora and forward and outward bending of the tibiae, the internal condyles of the femora being separated by 5 inches (12.7 cm.) when the internal malleoli were in contact. Examination of the central nervous system showed monoplegia of the left arm, with rigidity, increased reflexes and some general wasting. The left leg gave no evidence of paralysis except for a slight increase of the reflexes, as compared with the right leg. The plantar responses were normal; the abdominal reflexes were not obtained. The pupils were equal and regular. Accommodation and reaction to light were sluggish. Examination of the fundi revealed a small hemorrhage below and external to the left disk. Bilateral deafness of the middle ear was present. Examination of the cardiovascular system revealed thickening and tortuosity of the radial, brachial and temporal arteries, with visible pulsation. The systolic blood pressure was 120; the diastolic was indeterminate, pulsations being heard over the whole range down to zero. There was some cardiac hypertrophy. The apex beat was in the fifth space of the midclavicular line. A systolic murmur was audible at the base and apex of the heart. No thrill was present. Accentuation and roughening of the second aortic sound were found, but no diastolic murmur was heard. The pulse tended to be dicrotic, and aortic incompetence was suspected. Crepitations were heard at the bases of both lungs.

CASE 13.—E. R., a woman, aged 39, had experienced a vague aching over the whole back for two years. This had become increasingly more severe. The pain often started in the right lumbar region and gradually spread upward toward the shoulders, but during the last few months before examination it had been more severe on the left side. The pain was described as hot, gnawing and continuous, with periodic stabbing exacerbations. It was aggravated by exertion or by the carrying of heavy objects and was relieved when the patient lay down. A similar type of pain occurred in the knees and shins and, later, in the joints of the elbows. For eighteen months before examination the patient had felt that she was stooping and that her shoulders were becoming rounded. About a year before examination a masseuse at a Turkish bath noticed that the spine was bent. For twelve months the head had been growing larger, and the patient had to buy larger hats. For one year the eyesight for near objects had gradually deteriorated. Shortly before examination the pains in the back and limbs had become sufficiently severe to disturb the patient's sleep. Examination showed gross changes in the skull characteristic of Paget's disease; bulging of the temporal bones; a prominent occiput, with some enlargement of the vertex of the skull; marked prominence of both clavicles, with thickening and exaggeration of the anterior convexity, and slight thickening of the left humerus. The femora were apparently unchanged. There were a slight anterior convexity of the right tibia and marked kyphosis and some scoliosis, with apparent prominence of the ribs on the right side posteriorly. The costal angle was not increased. Examination of the cardiovascular system showed a blood pressure of 120 systolic and 70 diastolic. There was no evidence of any changes in the arteries; no cardiac hypertrophy was present, and the heart sounds were normal. No abnormalities of the central nervous system were found. Roentgenography confirmed the diagnosis of osteitis deformans.

CASE 14.—W. H., a man, aged 41, had pains in the lower limbs and the back for six years. These were aching in character and were worse when the patient walked. The pains in the legs were often acute, even at rest, and occurred in attacks lasting about half an hour at intervals of a few days. For five years the

patient had noticed bowing of the legs. A short time before he was examined he complained of general weakness. Examination showed some enlargement of the skull, with prominence of the frontal and parietal regions; moderate scoliosis, kyphosis and lordosis; thickened and prominent clavicles; a diamond-shaped abdomen with a wide costal angle; slight outward bending of the left radius, and gross outward and forward bowing of both femora and both tibiae, with bowing of the legs. Marked cardiovascular hypertrophy was present. The blood pressure was 160 systolic and 110 diastolic. The apex beat was in the sixth space, $\frac{1}{2}$ inch (1.27 cm.) external to the midclavicular line. Accentuation of the aortic second sound and thickening and tortuosity of the radial, brachial and temporal arteries were found. Examination of the central nervous system showed that the reflexes of the lower limbs were brisk; they were greater on the left than on the right. The plantar reflex was normal on the right but was not obtained on the left. On roentgenographic examination the skull showed the typical nigger-hair appearance of osteitis deformans, and the pelvis was typically dense, woolly, patchy and thickened. The appearance of the femora was typical: the cortex was bent and thickened, with areas of translucence, and the pattern and texture were accentuated. Typical changes were found in the tibia. The spine showed the typical dense and woolly appearance (Jupe). The Wassermann reactions was doubtfully positive.

CASE 15.—E. M., a man, aged 60, was admitted to the hospital because of a condition diagnosed as resolving appendicitis. It was noticed that the head was enlarged in a manner suggestive of osteitis deformans, and the patient stated that during the last eight years he had required progressively larger hats. The size which he was wearing at that time was $7\frac{1}{2}$, as contrasted with the original $6\frac{3}{4}$. For several years he had suffered from increasing deafness on the left side. Examination showed an enlarged skull, with bulging of the frontal and occipital regions, and a long ridge on the vertex; gross forward and outward bowing of the femora; saber-shaped tibiae; some bending of the humeri and radii, and a diamond-shaped abdomen with a wide costal angle. Examination of the cardiovascular system showed thickening of the radial and brachial arteries, with visible pulsation. The pulse was not markedly collapsing. The systolic blood pressure was 150, the diastolic, 0, the pulsation being heard right down to 0. The apex beat was not located. There was a systolic murmur in the mitral area; the sounds at the base of the heart were distant, and no diastolic murmur could be detected. The high pulse pressure suggested aortic incompetence. The central nervous system showed no abnormalities. The fundi were normal except for arteriosclerosis of the retinal vessels. There was deafness of the left middle ear. Roentgenography showed changes characteristic of osteitis deformans. The Wassermann reaction was negative.

CASE 16.—L. B., a woman, aged 60, had noticed bowing of the legs and vague, generalized pains for four years. Examination showed no gross changes in the head, although there was some bulging in the temporal region. Curvature of the ulnae was found, which was greater on the right than on the left, with decubitus valgus. Other findings were: marked outward and forward bowing of the femora, with genu varum; forward bending of the tibiae; gross enlargement of both clavicles, especially the right; a diamond-shaped abdomen with a wide costal angle and a broad pelvis, and bilateral arthritis of the knees, with some wasting and atonia. Examination of the cardiovascular system showed thick and tortuous radial, brachial and temporal arteries, a blood pressure of 120 systolic and 100 diastolic and some cardiac hypertrophy, with accentuation of the aortic second

sound. Examination of the central nervous system revealed slight convergent strabismus; otherwise no abnormalities were found. There was bilateral deafness of the middle ear. Roentgenography showed osteitis deformans.

CASE 17.—L. P., a woman, aged 55, stated that she had been bow-legged for many years, but not as a child. She was admitted to the hospital with a fracture of the middle third of the left femur, which had been caused by a fall from a chair. Examination showed that the skull was not obviously affected. There was gross outward and forward bowing of both femora, with genu valgum. Examination of the cardiovascular system showed gross thickening and tortuosity of the radial, brachial and temporal arteries, a blood pressure of 200 systolic and 110 diastolic, the apex beat in the fifth space $\frac{1}{2}$ inch (1.27 cm.) external to the midclavicular line and an increased aortic second sound. The central nervous system showed no abnormalities. The Wassermann reaction was negative.

CASE 18.—S. B., a woman, aged 50, had suffered for seven years from aching and shooting pains in the right leg, chiefly on the inner side of the tibia above the ankle. The pain was worse when she walked. During the last few years the pain had spread upward to the hip and the lumbar region. In 1925 the right tibia was found to be bent forward and greatly thickened anteriorly. There was tenderness of the bone and of the muscles of the calf. Linear osteotomy was performed by Sir Hugh Rigby and microscopic examination of the removed piece of bone showed changes typical of osteitis deformans. During the last few years before examination there had been some frequency of micturition, two times during the night and six times during the day; there was some difficulty and pain in beginning. Examination showed no obvious enlargement of the skull but revealed outward and forward bowing of both femora and anterior bending of the right tibia; well marked scoliosis, kyphosis and lordosis, with rigidity in the lumbar region; well marked thoracic sulcus with a wide costal angle; a diamond-shaped abdomen, and a broad pelvis. On examination of the cardiovascular system no gross changes were found in the arteries; the blood pressure was 130 systolic and 80 diastolic. In the central nervous system the optic disks, the pupils and the cranial nerves were found to be normal. There was no weakness, ataxia, dystonia or wasting of the upper limbs. The reflexes in the upper limbs were brisk and equal. There were diminished appreciation of pinprick, cotton-wool and heat on the left arm and some general weakness of the lower limbs, without wasting, ataxia or dystonia. The reflexes were brisk and equal, and there were diminished sensation to pinprick over the right leg and the outer side of the left leg and indefinite and patchy anesthesia and analgesia, which gradually became less defective on ascending toward the thigh. On both legs there was a marked defect in appreciating warmth; the defect continued onto the trunk, there being slight relative cutaneous anesthesia and analgesia up to the fifth thoracic level. The Wassermann reaction was negative. Roentgenograms of the skull and femora showed the characteristic changes of osteitis deformans.

CASE 19.—E. R., a man, aged 52, had had pains in all his joints, especially in those of the left hip, for several years. The pains were aching in character and occurred every day. At night he had noticed cramps in both legs, as if the muscles were being pulled apart. There was an increasing tendency to stoop, and the effort to stand erect was associated with much pain. There were also troublesome headaches, particularly in the occipital and temporal regions, and the head had gradually increased in size, requiring a $7\frac{3}{8}$ size hat, whereas the patient had formerly worn a $6\frac{7}{8}$ size. Increasing deafness had occurred during the year pre-

ceding examination. Examination showed a grossly enlarged head with marked prominence in the temporal and supra-orbital regions. Both femora were bowed outward and forward, and genu varum was present. The tibiae were not obviously affected; the clavicles were thickened; the spine showed marked kyphosis. Examination of the cardiovascular system showed gross thickening and tortuosity, with visible pulsation of the radial, brachial and temporal arteries, and marked cardiovascular hypertrophy, the apex beat being 1 inch (2.54 cm.) external to the midclavicular line. The blood pressure, however, was only 140 systolic and 60 diastolic. The central nervous system showed no abnormalities. There was bilateral otitis media. The Wassermann reaction was negative. Roentgenography gave positive findings.

CASE 20.—J. B., a man, aged 71, had had pains in the left thigh and knee for six years and had been unable to tolerate any pressure on the left knee. For two years there had been marked wasting and limitation of movement in the region of the left hip. For one year there had been slight headaches in the right temporal and retro-ocular regions and diplopia on looking to the left; apparently the latter feature was not constant. The head had been growing larger during the eight months preceding examination. More recently some deafness had been observed on the left side. The patient thought that there had been a tendency to bowlegs within the last few years; this had been more marked on the left side. Examination showed no gross changes in the skull. Movement of the left hip was limited in all directions. Other findings were: forward and outward bowing of both femora, with genu varum and separation of the internal condyles by 3 inches; a wide costal angle; a diamond-shaped abdomen, and a broad pelvis. Examination of the cardiovascular system showed moderate thickening and tortuosity of the radial, brachial and temporal arteries; a blood pressure of 160 systolic and 85 diastolic; slight cardiac hypertrophy, and bradycardia, with a pulse rate of 54. Examination of the central nervous system showed normal disks and pupils, diplopia on looking to the left and nystagmoid movements on extreme deviation to the right or left. The other cranial nerves were normal. The upper limbs showed no abnormalities. There was relative analgesia of the left leg over the third and fourth lumbar segments. The Wassermann reaction was negative. Roentgenography revealed thickening of the outer plate of the skull, with sclerosis. Atheromatous arteries could be seen. The changes in the skull were not more characteristic of Paget's disease than of syphilis. The changes in the bones of the pelvis and left tibia, however, were typical of osteitis deformans. There was osteo-arthritis of the left hip.

CASE 21.—F. G., a woman, aged 55, had experienced stabbing pains in both legs for five years. The pains traveled along the long axis of the limbs from the knee downward. They occurred several times a day and were of momentary duration. They sometimes caused the legs to give way and the patient to fall. Occasionally they lasted for several hours and were then of burning character, leaving a persistent soreness over the skin of the shin-bone. There were occasional vague pains in the upper part of the left arm. The patient also suffered from severe headaches during this period; these were throbbing in character and occurred over the right eye and in the occipital region; they were fairly constant. During the same period there had been gradual forward bending of the tibiae, the changes in the right tibia having begun one year before those in the left. For two years there had been frequency of micturition (two times at night and twelve times during the day), and failing vision. The menopause had occurred six years before examination. The patient had been treated for three years with suprarenal extract

in doses of 5 grains (0.32 Gm.) three times a day, with almost complete disappearance of pain. Examination showed no gross changes in the skull. There were forward and outward bowing of the femora and anterior bending of both tibiae, with genu varum; marked lordosis and kyphosis, with lumbar fixation, and some bending of the forearms, especially of the radii, which was greater on the left than on the right. Examination of the cardiovascular system revealed moderate thickening of the arteries, with cardiac hypertrophy. The apex beat was in the fifth space just external to the midclavicular line, and the blood pressure was 185 systolic and 110 diastolic. There was a tendency to myxedema. The central nervous system was normal.

CASE 22.—E. T., a woman, aged 53, had had symptoms consisting of pain in the left shoulder and forearms for several years. The pain was aching in character; it occurred only occasionally. The patient came under observation because of an inquiry into the family history of her brother, who was in the hospital (case 23). Examination showed no gross changes in the head, but there was some slight bulging of the occiput. The clavicles were enlarged and prominent; the left radius had a marked outward convexity and appeared to be somewhat elongated; the costal angle was not wide; the femora were bowed in an outward and forward direction, the condyles being separated by 2 inches (5.08 cm.); there were no gross changes in the tibiae. Examination of the cardiovascular system showed only a slight thickening of the arteries; the blood pressure was 120 systolic and 80 diastolic, and there was some accentuation of the aortic second sound. On roentgen examination the skull appeared to be rarefied, but unevenly so, so that a large parietal island of denser bone remained surrounded by some smaller dense areas; the differentiation between the inner and outer tables was well seen. The left femur was thickened in the upper two thirds, and osteitis was present. There was a lack of differentiation between the medulla and the compact layers. The right femur was similar to the left; there was a marked patch of rarefaction in the upper end about the greater trochanter. The left radius was elongated, thickened and apparently twisted, being overlong for its allotted space; the lower half was somewhat thinner and less dense, giving an appearance suggestive of osteitis fibrosa.

CASE 23.—G. L., a man, aged 49, had noticed gradual bending of the right forearm for ten years, the right wrist having become prominent. For eight years there had been a gradual increase in the size of the head; at the time of examination the patient wore hats size $7\frac{1}{2}$; formerly he had worn size $6\frac{7}{8}$. For one year there had been aching in the right leg after standing for a long while. The patient was admitted to the hospital complaining of severe pains in the right leg and thigh of one month's duration. The pains woke him at night and prevented much walking. The condition was found to be due to a pathologic fracture of the neck of the femur, of which there was no definite history but which was revealed by roentgen examination. The fracture was incomplete and not unlike a greenstick fracture; there was no displacement. Examination showed gross enlargement of the skull, with frontal bossing, which was greater on the right than on the left; sunken orbital fossae, and pronounced occipital protuberance. Both clavicles were enlarged. The right forearm was grossly distorted, the radius having a marked outward and dorsal convexity and the styloid processes of the ulna being especially prominent. The left arm appeared normal. There were marked kyphosis and lordosis, with slight scoliosis and prominence of the left scapula. The costal angle was wide, and the abdomen was diamond-shaped. The femora were bowed in a forward and outward direction, with genu varum and

separation of the inner condyle by $2\frac{3}{4}$ inches (6.9 cm.). The tibiae were not grossly involved. There was some creaking of the right knee. Examination of the cardiovascular system revealed: moderate thickening of the brachial arteries, a blood pressure of 145 systolic and 90 diastolic, the apex beat in the fifth space of the midclavicular line and some accentuation of the aortic second sound. The Wassermann reaction was negative. On roentgen examination the changes in the skull, femur and pelvis were found to be characteristic of Paget's disease, but the condition of the radius, as in case 22, bore some resemblance to osteitis fibrosa.

Special Note: This patient and the patient in case 22 were brother and sister, and therefore the cases are of interest in demonstrating a possible family incidence of osteitis deformans. It was also ascertained that curvature of the spine developed in the mother in middle age and that she had to wear a spinal jacket. She died at the age of 65, and, although it was impossible to obtain any further information, it seems not unreasonable to suspect that her condition was Paget's disease. Another interesting feature was the unilateral involvement of the radii in this and in the previous case, the left radius being involved in the left-handed patient and the right in the right-handed patient, thus apparently illustrating the effect of function on the development of curvature of diseased bones.

CASE 24.—M. L., a woman, aged 78, had noticed prominence of the left knee and pains in both legs for four years. The latter occurred mostly at night along the long axis of the limbs from heel to knee and were of a shooting character. The legs gradually became bent, and people observed that the patient's head was getting larger. For three years she had suffered from severe headaches of the vertex, which were "maddening" in character, like the pressure of a weight or the trickling of water. For two years she had frequency of micturition and urgency of defecation. She was able to walk quite well with the aid of a stick. Examination showed no gross changes in the skull but a slight bulging of the right frontal region. Some enlargement of the clavicles, slight decubitus valgus and a wide costal angle were found. There was marked forward bowing of the left tibia, but the right tibia was normal. There was also marked outward and forward bowing of the right femur and, to less extent, of the left. The spine showed no gross changes. Examination of the cardiovascular system showed: thickening and tortuosity, with visible pulsation of the brachial, radial and temporal vessels; the apex beat 1 inch (2.54 cm.) external to the midclavicular line and in the fifth space; accentuation of the second sound in the aortic area; a diastolic murmur to the left of the sternum; a systolic murmur in the pulmonary and mitral areas; a collapsing pulse; a blood pressure of 200 systolic and 40 diastolic, and aortic incompetence. Examination of the lungs showed scattered rhonchi. The central nervous system was normal. Roentgenography revealed marked changes in the tibiae and femora typical of osteitis deformans, with slight changes in the skull.

CASE 25.—J. B., a man, aged 50, had a pathologic fracture of the right tibia six years before examination. Since that time, he had had pains in the legs and forearms; these were gnawing in character and were eased by suprarenal extract. In addition he experienced dull, continuous, frontal headaches. For the three years preceding examination he had noted increasing prominence of his forehead. He was admitted to the hospital with a pathologic fracture in the proximal third of the femur, just distal to the lesser trochanter. For three years he had some frequency of micturition, two times at night and five times during the day. The skull showed bulging of both temporo-frontal regions and marked supra-orbital ridges. Both clavicles were thickened. A wide costal angle and a diamond-shaped

abdomen were found. There was slight outward curving of both femora, with bowlegs and saber-shaped tibiae. The lower end of both ulnae was prominent, especially that of the left, which was painful. Examination of the cardiovascular system revealed slight thickening of the arteries and tortuous temporal arteries. The apex beat was in the sixth space, $\frac{1}{2}$ inch (1.27 cm.) external to the mid-clavicular line. There was a systolic murmur in the mitral area. The blood pressure was 120 systolic and 80 diastolic. The central nervous system showed no abnormalities. Deafness of the right middle ear was present. The Wassermann reaction was positive. Roentgenography showed changes in the femur, tibia and skull characteristic of osteitis deformans, the skull being only slightly affected.

CASE 26.—M. H., a woman, aged 54, fell on her knee in 1924, and traumatic synovitis developed. Roentgen examination of the knee suggested osteitis deformans. Since that time the patient had had recurrent arthritis of the joint of the left knee. In 1927 further roentgenographs of the femora and tibiae showed typical osteitis deformans. Great relief of pain followed the administration of suprarenal extract. For several years a stoop had gradually developed, and a friend suggested that the patient was becoming bandy-legged. No gross changes in the skull were found on examination. Kyphosis, lordosis and decubitus valgus were present, without marked curvature of the radii. There were gross forward and outward bending of both femora and forward bending of the right tibia, with separation of the internal condyle by 2 inches (5.08 cm.) and creaking of the right knee. Examination of the cardiovascular system showed no gross thickening of the arteries. The pulse was not collapsing. The systolic blood pressure was 125, the diastolic, 0, the pulsations being heard down to 0. No diastolic murmur was heard in the aortic area or over the precordium. The aortic second sound was accentuated, but the apex beat was not displaced. Examination of the central nervous system gave negative findings. Roentgen examination of the femora and tibiae showed changes typical of Paget's disease. The skull was not affected.

CASE 27.—L. I., a woman, aged 63, had experienced pains in the legs, and to a less extent in the arms, for three years. These were throbbing and continuous and were worse at night and on exertion. There had been a marked increase in the size of the head, with prominence of the orbital and occipital regions, and the legs had become bowed. The patient had experienced dull, continuous frontal headaches, with throbbing of the temporal arteries, and formication over the head at night. There had also been cramps of the legs at night and occasional nocturnal frequency. Examination revealed: gross enlargement of the skull; bowing of both bones of the forearms, especially the ulnae; gross enlargement of both clavicles; marked forward and outward bowing of both femora, and anterior bending of both tibiae, with genu varum. Examination of the cardiovascular system showed thickening of the arteries, with visible brachial and temporal pulsation. The blood pressure was 110 systolic and 40 diastolic. At the pressure of 40 the pulsations became less loud but were continued down to 0. The apex beat was located in the fifth space of the midclavicular line. The aortic second sound had a slapping and prolonged character, but there was no diastolic murmur. On examination of the central nervous system the disks, pupils and cranial nerves appeared normal. The upper limbs were normal. Anesthesia and relative analgesia to cotton-wool and pinprick were present in both lower limbs and in the trunk, gradually decreasing up to about the second

dorsal vertebra. There was a similar deficiency in the appreciation of heat and cold. The vibratory sense and postural sensibility were normal. The knee jerks were present and were equal; the ankle jerks were sluggish; the plantar reflex was normal. Roentgenography showed generalized osteitis deformans.

CASE 28.—E. B., a man, aged 69, was admitted to the hospital for prostatectomy. Examination showed some forward bending of the right tibia, and when the patient was examined with the possibility of osteitis deformans in view several changes were observed. Questions elicited the facts that the patient had always worn large-sized hats ($7\frac{1}{4}$) but that during the last fifteen years there had been an increase in the size of the skull; he was wearing hats size $7\frac{3}{8}$ at the time of examination. His grandsons, aged $8\frac{1}{2}$ and 8 years, both required size 7 hats, but their skulls showed no abnormality on roentgenographic examination. The patient's back had gradually become bent during many years, but this had been attributed to his occupation of ship repairer. Three years before examination he had severe hematemesis and melena, preceded by dyspeptic symptoms which were thought to be due to gastric ulcer. For ten years he had cold feet and for four years cold, blue hands in winter. Examination showed no gross changes in the skull, but there was some bulging in the temporofrontal region. There were marked kyphosis and slight scoliosis, some thickening of the clavicles, thickening of the right humerus, slight outward bending of both forearms, a wide costal angle, a diamond-shaped abdomen, marked forward and outward bending of both femora, forward bending of the tibiae, gross thickening of the right tibia and genu extorsum, the condyles being separated by 4 inches (10.2 cm.). Examination of the cardiovascular system showed gross thickening and tortuosity of the radial and brachial arteries, with visible pulsation; slight tortuosity of the temporal vessels; the apex beat in the fifth space $\frac{1}{2}$ inch (1.27 cm.) from the midclavicular line; marked accentuation of the aortic second sound but no murmur; a blood pressure of 140 systolic and 90 diastolic by Pachon's method or by the mercury manometer. The blood pressure in the right ankle was 270 systolic and 150 diastolic; in the left, 220 systolic and 130 diastolic. Oscillometric oscillations indicated patency of the tibial arteries. There were medium moist sounds at the bases of both lungs. The central nervous system showed no abnormalities except loss of the sense of vibration in both lower limbs. Roentgenography showed marked changes characteristic of osteitis deformans in all the bones; the tibial vessels were visible in the roentgenogram. Examination of the blood showed a urea content of 0.04 per cent. A blood count showed 4,900,000 cells, with 60 per cent hemoglobin and a color index of 0.61 per cent. The leukocytes numbered 3,760, with 69.5 per cent neutrophils, 1 per cent eosinophils, 23 per cent small lymphocytes, 0.5 per cent large lymphocytes, 5.5 per cent large hyaline cells and 0.5 per cent granular basophilic cells.

CASE 29.—Y. V., a woman, aged 69, entered the hospital with a history of dyspepsia of three years' duration simulating that of gastric ulcer. She had epigastric pain one and one-half hours after meals with periodicity. She had chronic bronchitis. Examination showed moderate enlargement of the skull, with bulging of the occipital and parietal regions, which was greater on the right than on the left; moderate kyphosis and genu varum, with outward bending of the femora and forward bending of the tibiae, which was greater on the left than on the right. Examination of the cardiovascular system showed: moderate thickening of all the arteries; tortuosity of the temporal vessels; a blood pressure of 140 systolic and 80 diastolic; the apex beat in the fifth space of the midclavicular line, and a sys-

tolic murmur at the apex of the heart. Scattered bronchi were audible throughout the lungs. Roentgenography showed typical changes in the femora, tibiae and skull. A blood count showed 4,900,000 erythrocytes, with 73 per cent hemoglobin and a color index of 0.74 per cent, and 4,880 leukocytes, with 42 per cent neutrophils, 1 per cent eosinophils, 43 per cent small lymphocytes, 6.5 per cent large lymphocytes, 6.5 per cent large hyaline cells and 1 per cent coarsely granular basophils.

CASE 30.—H. L., a man, aged 63, had aching in the right thigh for three years. For two years he had noticed outward bending of the left leg below the knee. A few months before examination he sustained a pathologic fracture of the left tibia while running. The skull was apparently normal on examination. There were outward and forward bending and gross thickening of the periosteum of the left tibia, and slight bending of the right tibia and of the right femur. No gross abnormalities were found on examination of the cardiovascular system. The blood pressure was 120 systolic and 80 diastolic. Roentgenograms of the tibia and femur showed osteitis deformans.

CASE 31.—D. R., a man, aged 72, was admitted to the hospital because of vesical calculus. Frequency of urination and dysuria had been present for several years. Roentgenography of the bladder incidentally revealed changes characteristic of osteitis deformans in the pelvic bones and lumbar segments of the spine. Subsequent questioning elicited a history of stabbing pains in the feet and legs, which ran parallel to the long axis of the limbs and had occurred over a period of thirty years. During the last few years the back had become bent. Periodic frontal headaches associated with vomiting and suggestive of migraine had occurred up to the age of 40. Twenty-five years before the patient was examined, fracture of the left clavicle had occurred. Examination revealed gross kyphosis and some scoliosis; there were no other obvious changes. Examination of the cardiovascular system showed thickening, tortuosity and visible pulsation of the radial and brachial arteries; indefinite capillary pulsation; the apex beat in the fifth space 1 inch (2.54 cm.) external to the midclavicular line; a diastolic murmur in the mitral area, and accentuation of the aortic second sound. The blood pressure was 140 systolic and 80 diastolic; below 80 the pulsations were heard down to 0, but with markedly diminished intensity. The temporal vessels were not tortuous. Examination of the central nervous system showed loss of the vibratory sense in the right leg and a fibrillary tremor in both calves. Both hands showed evidence of chronic arthritis.

CASE 32.—J. H., a man, aged 52, had osteitis deformans plus spastic paraplegia. Eighteen months before examination he had noticed occasional twitching of the lower limbs; this occurred about once a week and lasted for one second or longer. The twitching consisted of a short jerk of the whole limb. Nine months before examination he experienced a gnawing pain (likened to lumbago) at the lower part of the back. This pain continued constantly and was worse on bending. Five months before examination the patient awoke in the middle of the night with pins and needles sensations in the right calf, and at that time he observed weakness of the right leg. In the morning the left leg also became weak; on attempting to rise the patient found that he could walk only with difficulty, and he was forced to return to bed. Within three days complete paralysis of both lower limbs gradually developed. At this time retention of urine and complete constipation also occurred. Catheterization was necessary for three weeks, during which time the patient was "light-headed," had attacks of violence and was unable to recognize friends. Cystitis, bed sores and thrombosis of the left femoral vein were complications.

The medical adviser stated that at the onset the patient had had complete flaccid paralysis of both legs and anesthesia up to the costal margin. After a few weeks there had been gradual improvement; power and sensation had partially returned in the legs, with some simultaneous recovery of sphincter control. At that time a troublesome bronchitis had developed, and the patient suffered from "heart attacks," with a rapid, irregular pulse, which was controlled by digitalis. Since the acute attack the condition of the patient had gradually improved in all respects. He was, however, unable to walk, although the sphincter trouble had disappeared. A numb, dragging feeling in both legs had persisted. The backache had disappeared with the onset of paralysis. Examination showed a well developed, healthy looking man. There was no gross alteration of the skull, but the occipital and temporal regions showed a slight bulging. Decubitus valgus was present and was more marked on the right. There was some widening of the costal angle. There were also slight forward and outward bowing of both femora, particularly of the right, and moderate kyphosis, with rigidity of the lower thoracic and lumbar regions. On the whole, the changes in the skeletal system were not particularly marked on clinical examination. Examination of the central nervous system showed normal disks, pupils and cranial nerves. There was no abnormality of the upper limbs, the reflexes being present and equal. The abdominal reflexes were present and equal. The lower limbs showed marked spastic paraplegia in flexion; the knee and ankle jerks were grossly exaggerated; the Babinski reflex was obtained in both feet, and ankle clonus was present. Postural sensibility was absent, and the vibratory sense was greatly diminished in both legs. There was inability to appreciate cotton-wool, pinprick, heat and cold below the fourth lumbar vertebra, with relative impairment of sensation above this level. Sensation was found to approach normal gradually as examination ascended to the level of the tenth thoracic segment. Jerky involuntary movements of the lower limbs occurred at intervals of from one to three minutes. There was no marked wasting. While the patient was in the hospital the paraplegia became more severe, with the disappearance of reflexes. Incontinence of the urine and feces also developed. Permission to perform laminectomy was refused by the patient. Examination of the cardiovascular system showed that the arteries of the arm were moderately thickened; there was some tortuosity of the temporal vessels. The heart was normal. The blood pressure was 165 systolic and 100 diastolic. The Wassermann reaction was negative for the blood and the spinal fluid. The spinal fluid was clear, with no cobweb; it contained 1 white cell per cubic centimeter, but there was a marked excess of protein—0.3 per cent. Roentgenography showed definite and extensive thickening of the vertebrae, especially of the sacral and iliac bones; the changes were those of osteitis deformans. There was much lippling in the thoracic region. The appearance of the skull was only suspicious, there being a few areas of thickened patches in the vertex. The right femur showed thickening in the upper portion and a cotton-wool appearance in the middle portion, with suggestive changes in the lower third. The tibiae, radii and ulnae showed slight changes. The roentgenographic diagnosis was osteitis deformans.

CASE 33.—F., a man, aged 60, gave a history of gradual enlargement of the skull, bowing of the legs and stooping, of many years duration. He had suffered from recurrent ascites for several years. Examination revealed gross enlargement of the skull, with bulging of the frontal and temporal regions; a wide costal angle; very gross outward and forward bending of both femora and both tibiae; genu extrorsum, and meningocele in the midfrontal region. Cardiovascular findings were: moderate thickening of the radial and brachial arteries, with

tortuosity of the temporal vessels; a blood pressure of 135 systolic and 80 diastolic; the apex beat in the fifth space, $\frac{1}{2}$ inch (1.27 cm.) from the external midclavicular line, and a systolic murmur in the mitral area. There was bilateral deafness of the middle ear. Examination of the central nervous system showed lateral nystagmus in both directions. The cranial nerves otherwise were normal. The upper limbs were normal. The abdominal reflexes were present and equal; the knee jerks were present and equal; the right ankle jerk was not obtained, while the left ankle jerk was just present. The plantar reflexes were normal, and postural sensibility was normal. Examination of the abdomen showed an enlarged liver one handbreadth below the costal margin. Gross ascites was present. Roentgenography showed typical changes in all the bones. The Wassermann reaction was negative.

CASE 34.—F. H., a man, aged 54, in 1921 noticed some stiffness of his knees, which impeded walking and necessitated stopping on the pavement. The pain disappeared when the patient sat or lay down and was attributed to rheumatism. This condition continued until three months before examination (April, 1927), when the stiffness increased over a period of a few days, after which there occurred a sudden and dramatic loss of the use of both legs when the patient was on the way home. He stated that he sank to the ground several yards from his house and literally crawled home. Since that time he would not trust himself to walk, as his knees might become stiff at any moment and he would collapse. He had been treated with hot air baths, massage and ultraviolet rays, without any obvious effect. His general appearance was that of a healthy man; the skull was enlarged, with well marked supra-orbital ridges. The patient wore a hat size $7\frac{3}{8}$, whereas eighteen years before he had worn size $6\frac{3}{4}$. The circumference of the head at the time of examination was $22\frac{3}{4}$ inches (57.8 cm.). Both clavicles were enlarged, the right to a greater degree than the left. There were slight kyphosis, a wide subcostal angle, with splaying of the lower ribs, and a transverse indentation in the midthoracic region. The upper limbs were not obviously affected. The lower limbs showed genu extrorsum, with both patellae turned outward. Both femora rotated outward, and showed an external and slightly forward convexity. The internal condyles were separated by 3 inches (7.6 cm.). There was some limitation of movement at both hip joints, especially on the left. The upper and lower ends of the tibiae appeared to be thickened; some crepitations were heard when the knee joint was moved. Examination of the central nervous system revealed that the left pupil was slightly larger than the right; the fundi and the cranial nerves were normal. The supinator, biceps and triceps jerks were produced and were equal. There was no dystonia, wasting, ataxia, loss of power, sensory loss or absence of postural sensibility in the upper limbs. The abdominal reflexes were not obtained. Spastic paresis of both lower limbs was found, which was greater on the right than on the left; the spasticity was especially marked in the adductor muscles. The knee jerks were slight and were greater on the right than on the left. The ankle jerks were not obtained. The Babinski plantar reflex was elicited on both sides. There were marked fibrillation and twitching of the quadriceps muscles and hamstring tendons, with generalized wasting. All the movements of the lower limbs were weak, especially those of the extensors of the knee joints, and dorsiflexion of the ankle was present. Relative analgesia and anesthesia to pinprick and cotton-wool respectively was present over the fourth and fifth lumbar segments, involving the sacral areas to a less extent and extending higher than the fifth lumbar segment, with a gradual decrease in severity up to the third thoracic segment. There was defective appreciation of heat and cold over approximately the same area; heat was not

felt at all as such, and in addition there was some confusion between hot and cold stimuli. Postural sensibility was absent on the right side and was impaired on the left. The vibratory sense was lost over the fourth and fifth lumbar segments. The patient was unable to stand with any stability and would fall if he attempted to walk; this instability was worse with the eyes closed. Examination of the cardiovascular system showed: moderate thickening of the arteries, with tortuosity of the temporal vessels; a blood pressure of 140 systolic and 70 diastolic; the apex beat in the fifth space of the midclavicular line; accentuation of the aortic second sound, and a systolic murmur at the base and apex of the heart. The lungs were normal. There was slight enlargement of the liver, and the prostate was moderately enlarged. A blood count showed: erythrocytes, 4,800,000, with 70 per cent hemoglobin and a color index of 0.72 per cent; leukocytes, 7,840, with 65.5 per cent neutrophils, 1 per cent eosinophils, 27 per cent small lymphocytes, 14.5 per cent large lymphocytes and 2 per cent large hyaline cells. Roentgenography showed typical changes of osteitis deformans in the spine, skull, femora, tibiae and clavicles; the radii and humeri were not affected.

AGE; SEX; FAMILIAL INCIDENCE

Age.—Osteitis deformans usually becomes manifest in middle life. It rarely occurs before the age of 30, but in one of Paget's² patients it began at the age of 28. Czerny's¹ patient was a man aged 22, and one of Stilling's⁴ patients was first examined at 21 years of age. Roberts and Cohen³ cited four supposed cases from the literature, in which the age of the patients was between 12 and 16, and they raised the pertinent question of mistaken diagnosis and of possible syphilis. Packard, Steele and Kirkbride⁵ found the average age to be 61, the youngest patient they saw being 39 and the oldest, 82. Stilling recorded a case in a patient who was first seen at the age of 92.

In the series studied by us the average age of the patients when they were first examined was 55; the youngest was 39 and the oldest, 78. The average age of onset was 46; the youngest patient was 30 and the oldest, 60.

Sex.—Packard, Steele and Kirkbride found from a study of the literature that cases were reported in forty-one males and twenty-four females. In the series studied by Roberts and Cohen the incidence was about equal for both sexes. In our thirty-four cases there were eighteen females and sixteen males.

Familial Incidence.—Paget was unable to trace any inherited tendencies. Roberts and Cohen, however, cited thirteen cases of familial incidence from the literature, and two of their own patients were sisters. Apparently the condition has not been noted in more than two generations. The patients in cases 22 and 23 of our series were brother and

4. Stilling, H.: *Virchows Arch. f. path. Anat.* **119**:542, 1890.

5. Packard, F. A.; Steele, J. D., and Kirkbride, T. S.: *Am. J. M. Sc.* **122**: 552, 1901.

sister, and from their statements it is probable that their mother also suffered from osteitis deformans.

MODE OF ONSET

Osteitis deformans is usually insidious in its onset and may be present for many years without the patient being aware of anything unusual.

In ten patients of the present series the first symptom was pain in the lower limbs; in two, pain in the back, and in two, headache. Fracture of a bone was the first sign in four cases. In three patients bending of the lower limbs first attracted attention and in one, bending of the forearm. In two instances the patients were admitted to the hospital because of spastic paraplegia, and in six patients osteitis deformans was discovered only on roentgenographic examination for the following disorders: synovitis, prostatic disease, bronchitis, vesical calculus and appendicitis. It is therefore important to remember that patients with osteitis deformans do not necessarily show the classic picture of the disease, and, further, that gross changes of the skull may be lacking for many years. Roberts and Cohen were of the opinion that only half of their sixteen patients showed sufficient clinical evidence of Paget's disease before roentgenograms were taken.

PAIN IN OSTEITIS DEFORMANS

Paget stated that "in its earlier periods and sometimes through all its course the disease is attended with pains in the affected bones, pains widely various in severity, and variously described as rheumatic, gouty or neuralgic, not especially nocturnal or periodical."

Pain occurred in twenty-four of the thirty-four patients of our series. The pains were usually in the back and lower limbs, but eight patients complained of severe headache. The latter occurred in any part of the skull and was of variable character, for example, dull and shooting, nagging, throbbing or "maddening like a weight." Arteriosclerosis and hypertension ought to be considered as factors in the causation of headache in osteitis deformans, as they are frequently associated with it.

Pains in the lower limbs may be very severe. In some of our patients they were knifelike, shooting up and down the long axis of the limbs; they lasted only a few minutes but were followed by residual soreness of several hours' duration. The pains were sometimes sufficiently severe to cause the lower limbs suddenly to give way and the patient to fall. They might be worse on exertion or might awaken the patient at night. In some patients they were dull and aching.

Cramps in the calves sometimes occurred at night, or a sudden pain might compel the patient to stop walking, as in intermittent claudication. These pains were probably due to coincident arteriosclerosis in the peripheral arteries.

Other patients experienced pains in the joints, probably due to complicating arthritis.

Pain in the back may be very severe; it may be associated with a gradually increasing stooping posture and may be aggravated by the attempts of the patient to stand up straight.

Elting⁶ suggested that pain in the long bones is due to distention of the periosteum. In some cases in this series pain was definitely associated with the changing shape of the bones and the development of new axes of strain and stress.

In several cases dried suprarenal extract in doses of 5 grains (0.32 Gm.) taken three times a day was very potent in relieving pain. Our attention was first drawn to this empirical therapy by Robert Milne. (Investigations of the effects of cortical extract parenterally administered are being carried out.)

SKELETAL CHANGES

There is little to add to the original description of Paget. The changes in the shape of the bones are dependent on softening and on the subsequent influence of gravity and muscular tension. The latter factor is well shown in patients 22 and 23 of the present series, a sister and brother. The brother was right-handed and had marked convex bending of the right radius. The sister was left-handed and had equally well marked bending of the left radius. The effect of gravity is shown by gradually increasing kyphosis, so that the face may habitually look toward the ground, and also by the bending of the femora and tibiae. The latter may be bent inward as well as forward so that they cross over one another, giving the appearance of scissor legs. This occurred in three of our patients (1, 9 and 10) and was so extreme in patient 10 that he had been unable to stand or walk for ten years. This is somewhat in excess of Paget's observations, as he wrote: "The limbs, however misshapen, remain strong and fit to support the trunk."

The wide pelvis has been frequently noted, but this is usually associated with a wide subcostal angle and splaying of the ribs. As the latter tend to approach the iliac crest, the bony boundary of the abdomen suggests the apposition of two faceted triangles—the diamond-shaped abdomen.

The classic picture of osteitis deformans, in which the patient resembles a simian-like ancestor, can hardly be mistaken. It is important

6. Elting, A. W.: Bull. Johns Hopkins Hosp. **12**:343, 1901.

to remember, however, that the skull may not be involved, at any rate, not for many years. Paget himself described such a case in a man, aged 51, in whom the disease began with changes in the tibia, but who showed no alteration in the skull ten years later. French⁷ observed an almost identical case in a woman, aged 53. Packard, Steele and Kirkbride, from a review of the literature, found that of sixty-six patients, nine showed no enlargement of the head. Of our series of thirty-four patients, gross changes in the skull were absent in no less than eight. In one patient (5) the skull only was involved, but this was more obvious roentgenographically than clinically.

As regards the bone which is first affected, Locke⁸ stated that this is "with few exceptions the tibia or the skull." Packard, Steele and Kirkbride found that in forty-nine cases (from the literature) the first bone involved was the skull in fourteen patients, one tibia in seventeen and both tibiae in thirteen. In the present series, apart from two cases in which the tibia showed changes five and seven years respectively before the other bones, evidence as to the sequence of skeletal changes was indefinite.

Fractures are not uncommon in osteitis deformans. They usually follow very slight traumas, but sometimes there is no obvious cause. Roberts and Cohen reported three fractures in sixteen cases. In a fourth patient roentgenography showed "no fewer than twenty incomplete fractures of the tibia on the convex anterior aspect." Fractures occurred in five patients in the present series; there was little or no preceding trauma in four patients. In three patients the femur was broken, and in two patients, the tibia. The ages of the patients at the time of fracture were 38, 44, 49, 54 and 63. In one patient (23) the neck of the femur was incompletely fractured, the injury resembling a green-stick fracture. The only complaint had been of aching of the thigh for one month, and neither the fracture nor osteitis deformans was suspected before roentgen examination. In one patient (2), a woman, aged 44, it was found necessary to plate the bone, as healing did not occur with external splinting. The fracture was in the middle third of the femur and had occurred while the patient was fastening her boot-lace. It is interesting to note that at operation the bone was found to be very soft. In another patient (4) the right femur was fractured six years after the left.

In regard to arthritis, Da Costa⁹ stated that "the joints are scarcely ever involved in the disease." Roberts and Cohen, however, found

7. French, H.: *Brit. M. J.* 2:1152, 1903.

8. Locke, E. A., in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1921, vol. 4, p. 408.

9. Da Costa, J. C.: *S. Clin. North America* 1:47, 1921.

osteo-arthritis in seven of sixteen patients. Knaggs¹⁰ discovered fairly frequent lipping of the vertebrae. Arthritis was present in at least three patients of the present series, but its presence is not regarded as of any significance, considering the age at which osteitis deformans commonly occurs.

Sarcoma developed in one patient (7) of the present series, the femur being the bone involved. Malignant changes were present in three of twelve of Paget's patients. Packard, Steele and Kirkbride, from a study of the literature, found sarcoma in five of sixty-seven patients, and Da Costa, from a similar study, noted sarcoma in fourteen of one hundred and fifty-eight patients.

LESIONS OF THE NERVOUS SYSTEM IN OSTEITIS DEFORMANS

Although the occurrence of nerve lesions in osteitis deformans has been noted by several authors, it is obvious from the diversity of the lesions that in the majority of cases they were merely coincidental: syringomyelia (Marie and Léri¹¹), tabes (Chartier and Descomps¹²), bulbar palsy (Lunn¹³), Huntington's chorea (Mackey¹⁴), lesions of the basal tract and spinal cord (Madea and de Fano¹⁵), lesions of the medulla (Gilles de la Tourette and Marinesco¹⁶) and lesions of the medulla and peripheral nerves (Hudelo and Heitz¹⁷). In other cases one must consider the possibility of compression by bony deformity: degeneration of nerves entering the intervertebral foramina (Pitres and Vaillard¹⁸), lesions of the posterior and lateral columns (Levi¹⁹), chronic myelitis (von Recklinghausen²⁰), increased reflexes and vesical disturbances (Pic²¹), spastic paraplegia (Azoulay, Lagrot and Ardin-Delteil,²² and Wyllie²³) and optic atrophy (Wyllie).

10. Knaggs, R. L.: *Inflammatory and Toxic Diseases of Bone*, New York, William Wood & Company, 1926.

11. Marie, P., and Léri, P.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **43**:904, 1919.

12. Chartier, M., and Descomps, P.: *Nouv. iconog. de la Salpêtrière* **20**:84, 1907.

13. Lunn, J. R.: *Tr. Clin. Soc. London* **18**:272, 1885.

14. Mackey, C.: *Lancet* **2**:787, 1906.

15. Madea, E., and de Fano, C.: *Morgagni* **47**:337, 1906.

16. Gilles de la Tourette, G., and Marinesco, G.: *Bull. et mém. soc. méd. d. hôp. de Paris* **2**:422, 1894.

17. Hudelo, and Heitz, J.: *Nouv. iconog. de la Salpêtrière* **14**:415, 1901.

18. Pitres, J. A., and Vaillard: *Arch. d. physiol. norm. et path.* **5**:106, 1885.

19. Levi, L.: *Nouv. iconog. de la Salpêtrière* **10**:117, 1897.

20. von Recklinghausen, F. D.: *Untersuchungen über Rachitis und Osteomalacie*, Jena, Gustav Fischer, 1910.

21. Pic: *Gaz. d. hôp. de Toulouse*, October, 1886.

22. Azoulay; Lagrot, and Ardin-Delteil: *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:920, 1923.

23. Wyllie, J. H.: *Brain* **46**:336, 1923.

Wyllie described two cases of paraplegia caused by compression, in which laminectomy was performed by Sir Percy Sargent. At operation "the bone was much thickened and softened. The perithecal space was absent, and the inner surface of the laminae lay in close apposition to the dura mater. Pulsation of the dura was at first very feeble but improved as the decompression was effected. In the patient who recovered from the operation, the paraplegic condition was greatly improved."

In two cases (32 and 34) of our series spastic paraplegia caused by spinal compression due to vertebral deformity was present. Both patients were admitted to the hospital because of possible spinal neoplasm. In patient 32 the first sign consisted of involuntary twitchings of the lower limbs. Subsequently pain occurred in the back and paresthesias of the lower limbs. Weakness began in the night, and within three days complete flaccid paralysis of the lower limbs, with retention of urine, had developed. Finally incontinence of urine, with spastic paraplegia, occurred. The sensory changes consisted of a gradually increasing impairment of sensation, descending from the level of the tenth dorsal vertebra, from partial loss to complete loss of sensation in the legs and feet. The cerebrospinal fluid was clear, showed no cobweb and contained 1 white cell per cubic centimeter and a marked excess of protein, 0.3 per cent.

In patient 34, apart from some preliminary stiffness of one knee, the onset was sudden weakness of the lower limbs. While he was walking home his legs gave way under him some yards from his house, and he was obliged to crawl home on all fours. Attempts at lumbar puncture were unsuccessful (as in one of Wyllie's cases), and this drew attention to bony changes in the spinal column and in other bones. The signs were those of spastic paraplegia, with sensory changes similar to those in patient 32. Permission for an operation was refused in both cases.

Seven other patients had evidence of nerve lesions, which were attributable to spinal compression or to vascular changes. Patient 5 had transitory paresis of both lower limbs, with relative analgesia. Patient 8 had involuntary twitching of the right foot; the reflexes in the lower limbs were increased but were equal on the two sides, and the plantar responses were equivocal. Patients 18, 20 and 25 had relative anesthesia and analgesia of the lower limbs, which gradually approached normal toward the trunk. Patients 28 and 31 had loss of vibratory sense in the lower limbs.

One patient (12) suffered from senile epilepsy. During the six months previous to examination he had three attacks of convulsions, with loss of consciousness. Generalized twitching occurred during the attack, without evidence of focal spread. The last attack resembled status epilepticus; there were repeated convulsions for four hours and a coma-

tose state persisting for two days. Examination revealed left hemiplegia, the upper limb being very much more involved than the lower. The blood pressure was not raised, but there were marked arteriosclerosis and hemorrhages in the fundi.

Two patients (2 and 20) had lateral nystagmus with diplopia. Three patients (21, 24 and 25) suffered from frequency of micturition.

Apart from mere coincidence, neurologic disorders in osteitis deformans are attributable either to compression caused by bony overgrowth or deformity or to arteriosclerosis.

PSYCHOSES IN OSTEITIS DEFORMANS

Paget,² in his original description, emphasized the absence of mental changes in osteitis deformans. "Even when the skull is highly thickened and all its bones exceedingly altered in structure the mind remains unaffected."

Since then, however, several instances of psychosis have been reported. The earliest was that of Lunn's¹³ patient, a man, aged 75, who was in an institution for four years, the exact nature of the psychosis not being stated. Prince²⁴ described a case of delusional insanity in a woman, aged 44. Fussell²⁵ reported senile dementia in a man, aged 78. Mackey¹⁴ described a case of Huntington's chorea in a man, aged 57, with mental deterioration, excessive emotionalism and impaired memory. Hann²⁶ had as a patient a woman, aged 60, with mental deterioration and attacks of unconsciousness. Paine²⁷ described a case in a man, aged 75, with hallucinations, delusions and dementia. Smith²⁸ described delusional insanity in a woman, aged 60, and the development of osteitis deformans in a woman, aged 80, who had been in an institution because of a psychosis since the age of 31.

Kaufman²⁹ cited three cases from the literature in which occurred: melancholia (Fitz³⁰), psychosis and mental deterioration (Moynan³¹) and maniacal delirium with epilepsy (Marie³²). He described four additional cases: delusions and hallucinations in a woman, aged 65, impaired memory and intellect and confusion in a man, aged 52, paranoia in a woman, aged 53, and an indefinite psychosis and suspected intracranial tumor in a woman, aged 46.

24. Prince, M.: *Tr. A. Am. Physicians* **17**:392, 1902.

25. Fussell, M. H.: *Tr. A. Am. Physicians* **17**:406, 1902.

26. Hann, G. R.: *Brit. M. J.* **1**:135, 1910.

27. Paine, F.: *Proc. Roy. Soc. Med.* **6**:72, 1912-1913.

28. Smith, L. H.: *J. Nerv. & Ment. Dis.* **68**:578, 1928.

29. Kaufman, M. R.: *Psychosis in Paget's Disease (Osteitis Deformans)*, *Arch. Neurol. & Psychiat.* **21**:828 (April) 1929.

30. Fitz, R. H.: *Tr. A. Am. Physicians* **17**:398, 1902.

31. Moynan, R. S.: *Ohio State M. J.* **24**:206, 1928.

32. Marie, A.: *Encéphale* **22**:475, 1927.

Hartfall³³ described delusional insanity in a man, aged 63. In eighteen other patients with osteitis deformans he found no evidence of mental change. Rutherford³⁴ reported delusional insanity in a man, aged 62.

In our series of thirty-four cases there were two instances (5 and 11) of mental abnormality: homicidal tendencies and periodic loss of memory in a man, aged 50, and delusional insanity and impaired intelligence in a woman, aged 70. Minor mental deterioration—for example, defective memory for recent events—is more common.

Psychologic alterations of this kind are probably no more common than in patients of middle age who have arteriosclerosis but who are unafflicted with Paget's disease.

CARDIOVASCULAR SYMPTOMS

Arterial degeneration is common in patients with osteitis deformans. Thus Knaggs¹⁰ stated: "Atheromatous arteries are almost a constant feature in these cases, and are seen even when the disease occurs in middle age." Locke⁸ was of the same opinion: "More or less generalised arterio-sclerosis may be regarded as an almost universal manifestation of the disease." Roberts and Cohen³ observed that "one is impressed by the frequency of calcification of the arteries shown by x-ray."

Of the present series of thirty-four patients, nineteen showed severe arteriosclerosis; six, moderate, and four, slight; in four patients, however, there was no clinical evidence of arterial degeneration. The patients with severe arteriosclerosis were nearly all over 50 years of age.

It is possible that arteriosclerosis occurs more frequently in osteitis deformans than in a control group of patients of similar age, but there is not sufficient evidence to warrant the theory that toxins or abnormal calcium metabolism is the direct cause of the arterial degeneration.

Hypertension was present in thirteen patients, the systolic pressure being 180 or more in seven, and between 160 and 180 in six. Eighteen patients had a systolic pressure of 140 or less. Arteriosclerosis and hypertension were not infrequently dissociated, the former occurring without the latter and vice versa. This is in keeping with the findings in any group of patients.

Aortic incompetence was present in three patients, one of whom was suffering from syphilis.

In five patients with arteriosclerosis the diastolic pressure was indeterminate, pulsations being heard down to 0; a systolic murmur was

33. Hartfall, S. J.: *Lancet* 2:68 (July 11) 1931.

34. Rutherford, W. J.: *Lancet* 2:350 (Aug. 15) 1931.

present in the aortic area, and pulsation of the peripheral arteries was easily visible. On repeated examination, however, no aortic diastolic murmur could be detected. In only one of the five was hypertension present.

Bradycardia was present in one patient and auricular fibrillation in another.

In one woman, aged 68, who had arteriosclerosis, senile gangrene of the toes developed, and pulsation was absent in the posterior tibial and dorsalis pedis arteries. A periarterial sympathectomy by W. S. Perrin resulted in limitation of the gangrene and permitted a subsequent local amputation.

OPHTHALMIC AND AURAL SYMPTOMS

Ophthalmic Changes.—Paget² described the occurrence of retinal hemorrhages in osteitis deformans, and Watson³⁵ noted extensive choroidal changes. In three of Vergne's³⁶ patients there was well marked choroidoretinitis. Coppez³⁷ found degeneration of the retina in four patients, with the occurrence of diplopia in one. Roberts and Cohen³ described choroiditis and retinal hemorrhage in one patient. Crystalline opacities were noted by Hurwitz,³⁸ Vergne and Coppez. Wyllie²³ recorded two cases with both optic atrophy and diplopia. He attributed the optic atrophy to compression of the optic nerve by bony overgrowth and the diplopia to injury of one or more of the ocular motor nerves by similar bony changes. Ormard³⁹ described choroiditis and hemorrhages in one patient, and Batten⁴⁰ stated that angioid streaks associated with choroidal disease had been noticed in Paget's disease by Juler and by Verhoeff.

In our series there were two patients with optic atrophy (5 and 10); in the former the atrophy was associated with diplopia; in the latter, with choroiditis. Diplopia also occurred in patients 2 and 20, together with nystagmus. Hemorrhages of the fundus were present in patient 12, and keratitis with corneal opacities in patient 11. Patient 1, who was shown before the meeting of the Association of Physicians, in 1930 by Dr. Evan Bedford, had subretinal hemorrhages. Mr. T. C. Summers reported that "surrounding the macula in a horseshoe-shaped manner, deep to the retina, is a large plum-shaped hemorrhage, seen in each eye, and probably situated in the choroid. At the macula were numerous folds with a few streak hemorrhages which, from their color, appeared to be

35. Watson, W. T.: Bull. Johns Hopkins Hosp. 9:133, 1898.

36. Vergne, J.: Ann. d'ocul. 140:321, 1908.

37. Coppez, I.: Arch. d'opht. 32:529, 1912.

38. Hurwitz, S. H.: Bull. Johns Hopkins Hosp. 24:263, 1913.

39. Ormard, A. W.: Lancet 1:973, 1931.

40. Batten, R. D.: Brit. J. Ophth. 15:279, 1931.

in the deeper layers of the retina. One surprising feature was that the retinal vessels appeared quite normal."

The ophthalmic changes in osteitis deformans are probably caused by (1) bony compression of the optic or the oculomotor nerves or (2) retinal arteriosclerosis. There is not sufficient evidence at present in favor of a hypothetical toxin.

Impairment of Hearing.—Locke⁸ stated that "a gradual impairment of hearing in osteitis deformans is the rule." He considered that bony compression of the labyrinth is an important factor. Gregg⁴¹ pointed out the possibility of pressure by bony overgrowth on any of the cranial nerves, including the auditory.

In our series ten patients had grossly impaired hearing, but in nine this was due to chronic disease of the middle ear. The remaining patient had bilateral otosclerosis.

BIOCHEMICAL OBSERVATIONS

According to Locke, if syphilitic lesions of the bones are excluded, osteitis deformans is the most common of the chronic diseases of bone. A similar statement was made by Da Costa.⁹ Yet there are on record very few investigations of a biochemical nature dealing with this disease. We include under the term "biochemical investigations" the study of such questions as the balance between the intake and output of dietary constituents, whether dietary deficiencies (or excesses) play a part in the onset of the disease, whether any abnormal changes occur in the nature and amount of the various chemical constituents of the tissues, particularly of the bones and of the blood, and to what extent such changes are specific for the disease. A brief account of what has already been done in the biochemical field will be given in the following paragraphs.

Changes in Chemical Composition of the Tissues.—(a) Bones: The most obvious pathologic changes in osteitis deformans are those in the bones, and a few chemical observations have been made by various investigators on specimens of bones obtained post mortem from patients with this disease. One of the almost invariable general observations is an increase in the percentage of organic matter and a diminution in the percentage of mineral matter (ash) in the bones. The fat content is usually increased. Whereas normal bone was found by Locke to have 37.8 per cent of organic matter, every bone in the patients with osteitis deformans which he studied showed organic matter varying between 42.6 and 48.5 per cent. The percentage of calcium content of the bone was invariably below normal, as was the magnesium content. The

41. Gregg, D.: Neurologic Symptoms in Osteitis Deformans (Paget's Disease), Arch. Neurol. & Psychiat. 15:613 (May) 1926.

diminution in the latter was striking; while the normal value is in the region of 0.8 per cent, the values found for magnesium oxide in the bones of persons with osteitis deformans varied between 0.14 and 0.68 per cent.

Hunter ⁴² quoted Turnbull as stating that there is only one definite histologic difference between osteitis deformans (Paget) and generalized osteitis fibrosa (von Recklinghausen). In the former disease there is tremendous resorption of bone associated with great apposition, the apposition preponderating, while in the latter disease the essential change is widespread resorption of bone, apposition being focal and relatively insignificant. From the figures already quoted it appears that the bone laid down in osteitis deformans is abnormal not only in architecture but also in chemical composition.

(b) Blood: Hunter ⁴² stated that in Paget's disease the serum calcium and the plasma phosphorus are approximately normal. This differentiates the disease from generalized osteitis fibrosa, in which the serum calcium is almost invariably above and the plasma phosphorus below normal. However, although there are, unfortunately, few records of these determinations in true Paget's disease, the tendency is for the calcium to be a little below and the phosphorus a little above normal. In a group of twelve patients with osteitis deformans the serum calcium varied between 8.2 and 9.8 mg. per hundred cubic centimeters, with an average of 9.1 mg., while the plasma phosphorus varied between 2.7 and 5.3 mg., with an average of 3.7 mg. Normal figures for serum calcium by the method used (Clark-Collip) are usually between 9 and 11 mg., with an average of about 10 mg. For plasma phosphorus, the average is about 3.3 mg. If there is any real variation from the normal in either serum calcium or plasma phosphorus in Paget's disease it must be small.

From the content of calcium and phosphorus in the blood there is no definite evidence of any parathyroid disturbance, and most pathologists are agreed that it is unusual to find signs of increased parathyroid activity post mortem.

The most striking biochemical difference that has been found (Kay ⁴³) between the blood of patients with osteitis deformans and that of normal persons is the greatly increased phosphatase activity in the plasma in the former. It has already been reported by Kay ^{43a, b} that this enzyme is present in relatively large amounts (twice the normal or more) in generalized diseases of the bone other than osteitis deformans, namely, in generalized osteitis fibrosa (two cases), in osteomalacia (two

42. Hunter, D.: *Quart. J. Med.* **24**:433, 1931.

43. Kay, H. D.: (a) *Brit. J. Exper. Path.* **10**:253, 1929; (b) *J. Biol. Chem.* **89**:249, 1930; (c) *ibid.*, p. 235; (d) *Physiol. Rev.* **12**:384, 1932.

cases), in renal rickets (two cases), in adolescent rickets (one case) and in infantile rickets (in at least eight of ten cases). In almost all types of disease which did not involve the bone or in which the lesions of the bones were purely local, the phosphatase was either normal or slightly increased. The large rise in the phosphatase content of the plasma was thus almost specific for generalized disease of the bones.

*Plasma Phosphatase in Osteitis Deformans**

Case	Age, Years	Sex	Diagnosis	Duration, Years	Plasma Phosphatase Value†
1	57	F	Osteitis deformans, extensive changes.....	17	At least 3.00
2	44	F	Osteitis deformans, moderately extensive changes	6	At least 1.00
3	40	M	Osteitis deformans and meningovascular syphilis..	2	At least 1.30
4	62	M	Osteitis deformans, moderately extensive.....	5	1.50
5	50	M	Osteitis deformans, unusual type, skull only; changes in skull only seen on roentgen examina- tion; no other skeletal changes	?	0.40
6	49	F	Osteitis deformans, moderate changes only.....	5	1.30
8	49	F	Osteitis deformans, almost entirely in skull, marked	10	At least 1.30
9	54	F	Osteitis deformans, marked in all bones.....	11	At least 3.00
10	60	M	Osteitis deformans, extensive.....	30	At least 2.50
13	39	F	Osteitis deformans, skull, clavicles, spine.....	2	At least 2.50
14	41	M	Osteitis deformans, extensive changes in all bones	6	At least 1.40
15	60	M	Osteitis deformans, all bones involved.....	8	At least 2.80
19	52	M	Osteitis deformans, many bones affected.....	Several	At least 1.40
20	71	M	Osteitis deformans, general.....	6	At least 0.80
21	55	F	Osteitis deformans, many bones affected.....	5	At least 1.20
23	49	M	Osteitis deformans, familial.....	10	0.66
25	50	M	Osteitis deformans, many bones and skull slightly affected	5	1.13
L. 1	65	M	Clinically, carcinomatosis; roentgenologically, doubtful Paget's disease	2	0.43
26	54	F	Osteitis deformans, many bones affected but not skull	Several	1.20
28	69	M	Osteitis deformans, extensive changes.....	Several	At least 0.70
29	69	F	Osteitis deformans, extensive changes.....	3 (?)	1.90
30	63	M	Osteitis deformans, limited to bones of leg.....	3	1.30
L. 2	49	M	Osteitis deformans, slight changes only.....	3	At least 0.65
T. 1	64	F	Osteitis deformans, extensive changes.....	Several	1.70
T. 2	35	M	Osteitis deformans, marked changes, limited to bones of leg	?	At least 2.25

* The peak of the distribution curve for normal persons is 0.14; for persons with diabetes, from 0.17 to 0.21; for persons with renal disease, from 0.13 to 0.21; for persons with arthritis, 0.13; for persons with a neoplasm (excluding a renal neoplasm), 0.21; for persons with hyperthyroidism, 0.41, and for those with osteomyelitis, 0.27.

† Milligrams of phosphorus liberated from sodium glycerophosphate under standard conditions by 1 cc. of plasma.

The rise in the phosphatase of the blood in osteitis deformans was corroborated by Roberts,⁴⁴ who used whole blood for his determinations.

In all the thirty patients with Paget's disease in whom we determined the phosphatase content the value for plasma phosphatase was much above the normal, and in the majority of cases it was more than ten times the normal. It is worthy of note that in one of the two cases in which the plasma value was below 0.6 unit the diagnosis of Paget's disease was doubtful.

44. Roberts, W. M.: Brit. J. Exper. Path. **11**:90, 1930.

The method of determination of phosphatase used by us is that described by Kay.^{43c} The possible significance of the dramatic increase in plasma phosphatase in generalized disease of the bones and the connection of this agent with the similar enzyme which is known to occur in relatively large amounts in normal bone have recently been discussed by one of us (Kay^{43b, d}), and there is at present little to add, except to mention that the rise is capable of reversal after suitable treatment in certain cases of osteomalacia and generalized osteitis fibrosa. But so far we have not observed any definite diminution in plasma phosphatase in Paget's disease, either with or without treatment. Roberts⁴⁴ stated that he was unable to diminish the high phosphatase content of whole blood in osteitis deformans by any method of therapy which he employed.

Although the phosphatase content is definitely high in every patient with osteitis deformans examined, even when the history is short and the disease is in the early stages, yet there is a rough correlation between the amount of the enzyme per unit volume of plasma and the severity of the disease, in that the cases which, clinically speaking, are milder usually show lower values than the more severe or extensive cases, the latter invariably giving high values. The phosphatase content remains high for the duration of the disease; for example, in one case of eight years' standing, in another of seventeen years' and in another of thirty years' standing, the level of phosphatase was about the same as in a severe case of only two years' duration.

Of the twenty-five cases enumerated in the table, twelve have already been reported briefly as having shown a high content of plasma phosphatase (Kay^{43b}). These cases are included in this table as they have since been studied more thoroughly from a clinical point of view and in several instances the plasma phosphatase has been redetermined. The remainder are cases which were not previously studied for the determination of this enzyme. In spite of the high phosphatase content of the plasma, the urinary excretion of the enzyme, which has been determined in a few instances, remains low. The fecal excretion of the enzyme has not been followed.

The phosphorus partition in the blood was determined in one case only (13) by the method described by Kay and Byrom.⁴⁵ The figures were as follows: total acid-soluble phosphorus, 27.2 mg. per hundred cubic centimeters of blood; organic acid-soluble phosphorus, 23.9 mg. The hematocrit reading was 38.5 per cent corpuscles; the phosphorus index was 62, or slightly above normal. In three cases the phosphoric ester content of the plasma was determined and was found to be normal.

45. Kay, H. D., and Byrom, F. B.: *Brit. J. Exper. Path.* 8:240, 1927.

The method of phosphatase determination just described was recently applied by Race,⁴⁶ who found that in a fairly large group of patients in whom disease of the bone was suspected, the method was of value as an aid in diagnosis in the early stages before the clinical symptoms were sufficiently advanced to permit a positive statement. O'Reilly and Race,^{46a} in an interesting recent article described findings obtained for serum calcium, phosphorus and phosphatase in twenty-one cases of osteitis deformans. They found that, whereas the serum calcium and phosphorus are usually within normal limits, the phosphatase is always increased. The suspension stability of the blood is normal.

Changes in Mineral Metabolism.—With such obvious disturbance in skeletal structure it is only to be expected that the mineral metabolism will be severely disturbed during the course of this disease. We ourselves have not conducted any experiments on metabolism, but take this opportunity of bringing together a short summary of the results obtained in the few cases of Paget's disease in which experiments of this nature have been made.

In 1904, McCrudden, Goldthwait, Painter and Osgood⁴⁷ (quoted by Da Costa, Funk, Bergeim and Hawk⁴⁸) found a retention of 6 per cent of calcium during a seven day period in a patient with osteitis deformans. Gruner, Scrimger and Foster,⁴⁹ while studying a patient suffering from osteitis deformans, found a loss of nitrogen, phosphorus, calcium and magnesium. Complete analyses of the feces were not made. However, sarcomas were developing at the same time, and the patient died in a very emaciated condition a few months later. It is doubtful whether the results of this investigation have much bearing on metabolism in an uncomplicated case of Paget's disease.

Da Costa and his associates⁴⁸ made a thorough metabolic study in two cases of osteitis deformans, one advanced, the other in the early stages. In both cases there was pronounced retention of calcium; in one case 50 per cent of the daily ingestion of 1.6 Gm. (reckoned as calcium oxide) was retained; in the other, 18 per cent of the daily ingestion of 2.6 Gm. was retained. This is the opposite of the findings in osteitis fibrosa. In both cases the amount of calcium excreted in the urine was much lower than normal. In normal persons about 10 per

46. Race, J.: Arch. M. Hydrol. **10**:6, 1932.

46a. O'Reilly, T. J., and Race, J.: Quart. J. Med. **1**:471, 1932.

47. McCrudden, F. H.; Goldthwait, J. E.; Painter, C. F., and Osgood, K. B.: Am. Med. **7**:547, 1904.

48. Da Costa, J. C.; Funk, E. H.; Bergeim, O., and Hawk, P. B.: Pubs. Jefferson M. Coll. & Hosp. **6**:1, 1915.

49. Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: A Clinical and Histologic Study of a Case of Paget's Disease of the Bones with Multiple Sarcoma Formation, Arch. Int. Med. **9**:641 (June) 1912.

cent of the excreted calcium is found in the urine, but in one of these patients only 4.6 per cent, and in the other, only 1 per cent, of the total amount of calcium excreted was found in the urine. This, again, is the opposite of what occurs in generalized osteitis fibrosa. White also reported a case in which the amount of calcium excreted in the urine was markedly subnormal.

Phosphorus was also retained in both patients of Da Costa and his associates. The first patient retained 33 per cent of a daily intake of 4 Gm. (reckoned as phosphorus pentoxide), the second, 29 per cent of a daily intake of 4.3 Gm. The same was true of magnesium; 59 per cent of a daily ingestion of 0.4 Gm. was retained in the one case, and 35 per cent of a daily intake of 0.6 Gm. was retained in the second. Sulphur and nitrogen, on the other hand, were lost in the first (severe) case to the extent of 44 per cent of the intake of 0.6 Gm. of sulphur and 1 per cent of the intake of 9 Gm. of nitrogen, but the second patient retained a little sulphur and nitrogen.

Locke stated that in two of his patients on whom metabolic studies were carried out retention of calcium (19.4 per cent and 11.5 per cent) and of magnesium (19.9 per cent and 10.9 per cent) were observed. He did not find, however, that the amount of calcium excreted in the urine was abnormal.

Another careful study, this time of a single typical case of osteitis deformans, was made by Cuthbertson.⁵⁰ His results confirm those of Da Costa and his associates. There was a retention of 15 per cent of the intake of calcium, of 7 per cent of the intake of phosphorus and of 10 per cent of the intake of magnesium. As in the severe case studied by Da Costa and his associates, there was a distinct loss of sulphur, to the extent of 17 per cent of the ingested sulphur.

Both Da Costa and his associates and Cuthbertson arrived at the conclusion that new tissue was being laid down in osteitis deformans which was relatively richer than normal bone in calcium and magnesium and poorer in phosphorus. A portion of this retention might be concerned with the calcification of the arteries which was proceeding, and Da Costa and his associates quote Selig's⁵¹ statement that there is relatively much more magnesium in calcified arteries than in bone.

In summing up the situation with regard to mineral metabolism, Da Costa and his collaborators suggested that in advanced osteitis deformans the first step in the new formation of bone or osseous tissue is the production of a highly sulphurized organic matrix, which is transformed gradually by a process of calcification accompanied by the deposition of calcium, magnesium and phosphorus. During this deposition the sulphur

50. Cuthbertson, D. P.: *Glasgow M. J.* **108**:218, 1927.

51. Selig, A.: *Verhandl. d. Cong. f. inn. Med.* **25**:333, 1908.

of the matrix is replaced to a lesser or greater extent by the other elements mentioned, producing the results found experimentally, namely, retention of calcium, magnesium and phosphorus and loss of sulphur. These investigators suggested that a chronically somewhat decreased activity of the thyro-parathyroid mechanism may be concerned in the etiology of osteitis deformans. They pointed out that the metabolic picture of osteitis deformans is to a certain degree the reverse of that seen in parathyroid hyperplasia. If this theory is strong enough to bear additional speculation, it may be remarked that it has been shown that the amount of functional parathyroid tissue appears to vary greatly in apparently normal animals of the same species (Taylor, Weld, Branion and Kay⁵²). This may be true for man and may be the congenital factor which is concerned in the not infrequently familial character of Paget's disease. Nevertheless, so far as we are aware, no cases of Paget's disease have been recorded following partial thyroidectomy with its usual accompanying loss of parathyroid tissue.

We may summarize our biochemical information with regard to osteitis deformans as follows:

1. There is a diminished percentage of ash in the bone, which contains a much smaller percentage of calcium and magnesium than normal (Locke), though, owing to the immense size of the bone, the total calcium and magnesium content may be greater than normal.

2. The serum calcium is not increased above normal but may, on the contrary, be slightly below normal. The plasma phosphorus is possibly slightly above normal. The plasma phosphatase is almost without exception definitely increased.

3. In two advanced cases (that of Da Costa and his associates and that of Cuthbertson) there was pronounced retention of calcium, magnesium and phosphorus in the body, with loss of sulphur. In one milder case there was a less marked retention of calcium, magnesium and phosphorus with no loss of sulphur.

ETIOLOGY

Paget² believed osteitis deformans to be a chronic inflammation, as the term indicates. Knaggs¹⁰ thought that a toxin is responsible. Jefferson⁵³ suggested "an upset of internal secretion, thyro-parathyroid." Roberts and Cohen⁸ noted that in a few cases changes had been observed in the parathyroid gland at autopsy, but they quoted Erdheim's⁵⁴ view that the changes are secondary to increased calcium

52. Taylor, N. B.; Weld, C. B.; Branion, H. D., and Kay, H. D.: *Canad. M. A. J.* **25**:28, 1931.

53. Jefferson, G.: *Brit. J. Surg.* **3**:219, 1915-1916.

54. Erdheim, J.: *Frankfurt. Ztschr. f. Path.* **7**:175, 1911.

metabolism and are not etiologically connected with Paget's disease. The estimations of calcium in our series do not give any definite indication of constant hyperactivity or hypo-activity of the parathyroid glands. There is, perhaps, some suggestion of varying activity of these glands in different phases of the disease, although adequate biochemical examination of the calcium balance over long periods is the only method of determining this with certainty. Clinical and pathologic evidence indicates phases of softening and hardening of the bones, rarefaction and excessive calcification. Further, the same bone or different bones may show evidence of different phases of the pathologic processes. If the parathyroids or other ductless glands are primarily at fault, it would be difficult to explain cases in which only one bone was involved for as long as ten years. One would expect a constant generalized involvement, such as occurs in osteitis fibrosa associated with hyperparathyroidism. In the latter condition the content of blood calcium is almost invariably above normal and the content of blood phosphorus is low (Hunter ⁴²). This is not so in osteitis deformans. Erdheim suggested that any changes in the activity of the parathyroids that can be demonstrated are probably secondary to the gross bony changes that are occurring. Certainly there is insufficient evidence at present to support the hypothesis that parathyroid dyscrasia is the sole factor in the production of osteitis deformans. The hypothesis of a low grade chronic inflammation, although acceptable from some points of view, is not susceptible of easy proof.

A syphilitic origin of osteitis deformans has been urged by Lannelongue,⁵⁵ Fournier ⁵⁶ and many other French investigators. Da Costa and his associates, from a study of the literature, found that a positive Wassermann reaction was obtained in seven cases and a negative reaction in twenty-seven cases. Roberts and Cohen found that only two of their seventeen patients gave a positive Wassermann reaction. Elsner ⁵⁷ stated that no patient with an uncomplicated case of Paget's disease has given a positive Wassermann reaction. In our series of thirty-four patients, positive Wassermann reactions were obtained in three. We believe, therefore, that the evidence is definitely against the suggestion of a syphilitic origin of osteitis deformans.

A neurotrophic origin of osteitis deformans has also been advanced. Thus, in 1883, Lancereaux ⁵⁸ suggested that the nervous system plays an important rôle in the production of osteitis deformans. In 1894, Gilles de la Tourette and Marinesco,¹⁶ and, in 1902, Prince,²⁴ urged the

55. Lannelongue, M.: Bull. Acad. de méd., Paris **49**:299, 1903.

56. Fournier, M.: Bull. Acad. de méd., Paris **49**:532, 1903.

57. Elsner: New York State J. Med. **10**:287, 1910.

58. Lancereaux, E.: Traité d'anatomie pathologique, Paris, A. Delahage & E. Lecrosnier, 1885, vol. 3.

etiologic significance of the changes in the central nervous system. It is true that the neurotrophic origin of bony changes is accepted in tabes and syringomyelia and that lesions of the central nervous system have been described in osteitis deformans. The latter, however, are so diverse in their character and distribution as to render their etiologic significance doubtful. It is much more reasonable to regard them either as the result of compression or of arteriosclerosis or as merely coincidental.

ROENTGENOLOGIC SECTION

BY G. E. VILVANDRÉ

The roentgen changes in typical Paget's disease are characteristic and are easily recognized. The roentgenologic detection of cases unsuspected clinically and the more difficult differential diagnosis deserve discussion.

On several occasions patients who were referred to the x-ray department of the London Hospital for renal or urinary calculi were found to exhibit bony changes in the pelvis characteristic of osteitis deformans. The "cotton-wool" changes immediately attract attention. There may be enlargement of the whole pelvis, with encroachment on its cavity, and flattening may be present. Rarefaction is seen side by side with increased density in the iliac bones—a combination of osteoporosis and hyperostosis, destructive osteitis and productive osteitis. The neck of the femur may also be increased in width and density and may lose its sharpness of outline.

The lumbar part of the spine shows thickening, increased density and loss of sharpness, but the contrast of the areas of rarefaction and sclerosis is nothing like that in the pelvis, where the ischiopubic rami may show a marked increase in width and alteration in bony texture. At first sight the lower portion of the pelvic girdle may suggest carcinomatosis, but the increase in width and the patchy sclerosis are opposed to such a diagnosis. In Paget's disease both the medullary and the cortical portion may become involved. The new bone is at first osteoid, but it may become calcified, and softening may be followed by regained rigidity. Owing to the formation of new bone in osteitis deformans the skeleton increases in width, a change not present in secondary carcinomatosis, and a distinguishing feature.

The earliest evidences of metastatic carcinoma from the prostate are noted in the ilium along the margins of the sacro-iliac synchondrosis and give rise to an increased density of the bone. Such a condition must be differentiated from Paget's disease. Confusion of these conditions has not been an uncommon mistake. The more commonly affected bones are the pelvis, tibia and cranium. In the cases which came under observation because of the possible presence of calculus the clinical appearance of osteitis deformans was absent or slight. Occasionally,



Fig. 1.—Roentgenogram of the pelvic bones of a patient with osteitis deformans, showing increase in density, striations and cotton-wool appearance. The ilium and femur on the right side show osteoclastic changes, and fracture has taken place through the neck of the right femur.

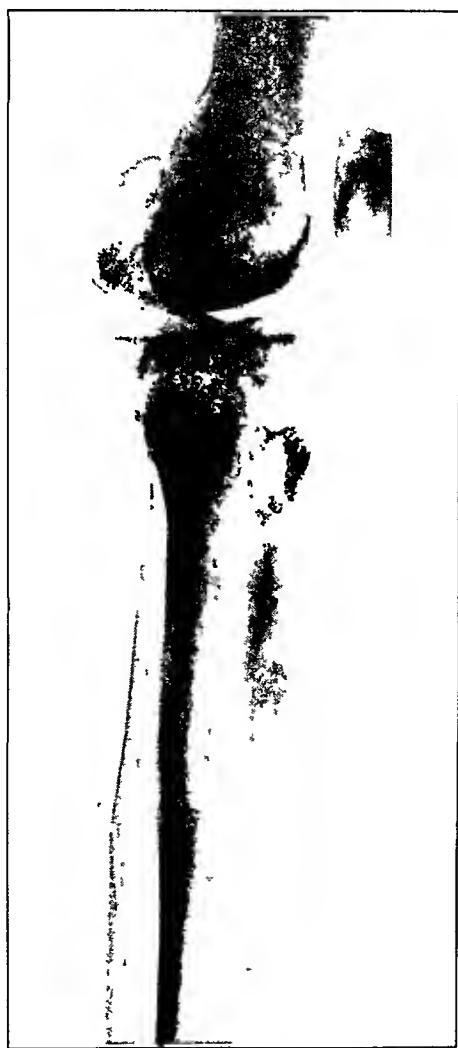


Fig. 2.—Roentgenogram showing the osteoclastic condition of the right femur and changes in the upper part of the tibia in the same patient as in figure 1.

patients with indefinite rheumatic pains have shown roentgenographic evidence of osteitis deformans, although clinically there was little to support the diagnosis. In some cases there has been no obvious enlargement of the skull; yet roentgenographic examination has revealed changes characteristic of osteitis deformans. The complication of the formation of sarcomatous tumors has been rare. In one case tumors of this kind occurred in the skull. The first tumor receded under treatment with roentgen rays, but others formed, and ultimately the patient died. Numerous partial fractures may be found in Paget's disease, especially along the anterior surface of the tibia. They are to be seen as transverse lines at right angles to the shaft. But in Paget's disease spontaneous fracture is rare. When it takes place the formation of callus and union may be very slow. The cortex, which early in the disease is often rarefied, owing to osteoclastic resorption, may and often does become denser, because of the excessive formation of bone subsequently laid down by osteoblasts, and the thickness of the bone also increases by subperiosteal formation. This is an important point in the differential diagnosis between osteitis deformans, osteitis fibrosa and secondary prostatic carcinoma. In the first disease the width of the skeleton is increased, and the shaft of the long bones may show much increase in weight. The presence of soft osteoid tissue leads to bending of the bones located where weight is prevalent such as the tibiae and femora and, of course, gives the well known appearance of Paget's disease in established cases. Bending may be observed also in the cervical part of the spine, and a close apposition of the occipital bone to the spinous process of the atlas may sometimes be seen. Spinal kyphosis may occur, and ankylosis of the vertebrae may follow, with resulting rigidity.

Calcification of the arteries is a common observation in Paget's disease. The femoral artery, as well as the arteries of the pelvis, often show considerable thickening.

Illustrative Cases.—CASE 23.—This patient exhibited most extensive evidence of osteitis deformans. The bones of the pelvis were increased in density and showed marked striations and a typical cotton-wool appearance (fig. 1). Extensive resorption was present on the right side of the pelvis, the ilium and the femur being affected to such an extent that fracture had taken place through the neck of the right femur. Increase in the width was evident, as is often the case in Paget's disease. The shaft of the femur showed marked absorption, but an increase in the cortex was evident, and the deposition of new bone in the periosteum was plainly seen. It is interesting to note the difference in the density of the two femora, the left one showing the result of osteoblastic repair, whereas the right showed the osteoclastic condition (fig. 2).

The upper half of the tibia showed marked changes, and the skull showed extensive thickening and enlargement (fig. 3). There was also some increase in the size of the pituitary fossa, and the typical signs of Paget's disease were present.

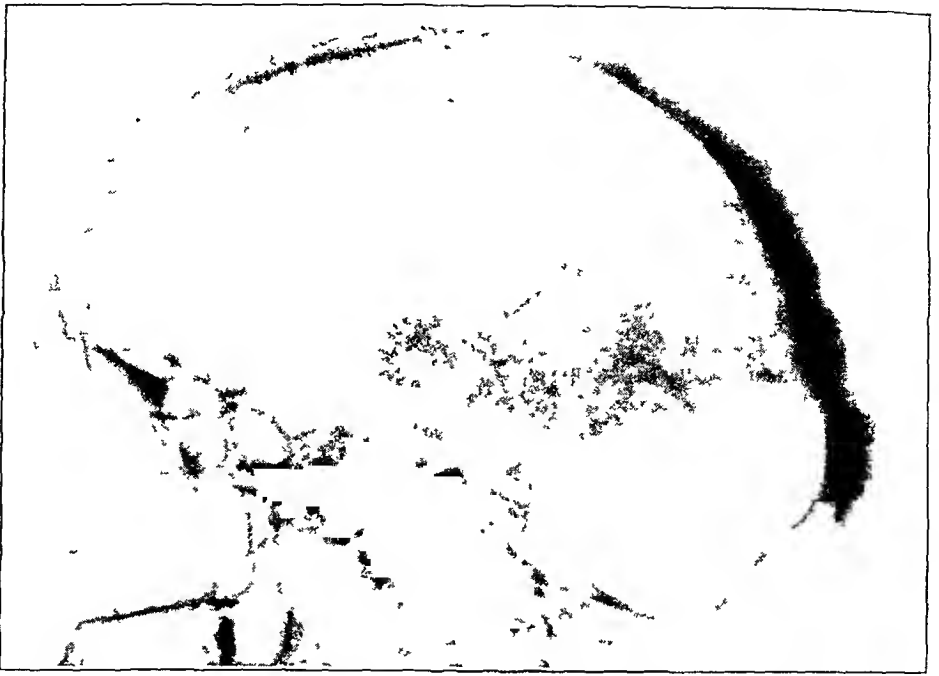


Fig. 3—Roentgenographic appearance of the skull, showing typical changes of osteitis deformans.



Fig. 4.—Roentgenogram of the bones of the forearms, showing softening, increased density and bending of the right radius in osteitis deformans

The skull was nearly an inch in thickness in the posterior portion. Softening of the long bones had taken place, especially of the right radius, in which definite bending was present (fig. 4). Here the medullary portion and the cortex were not differentiated, and areas of rarefaction appearing cystic were evident. The bone was increased in width, and, on the whole, a definite increase in density was

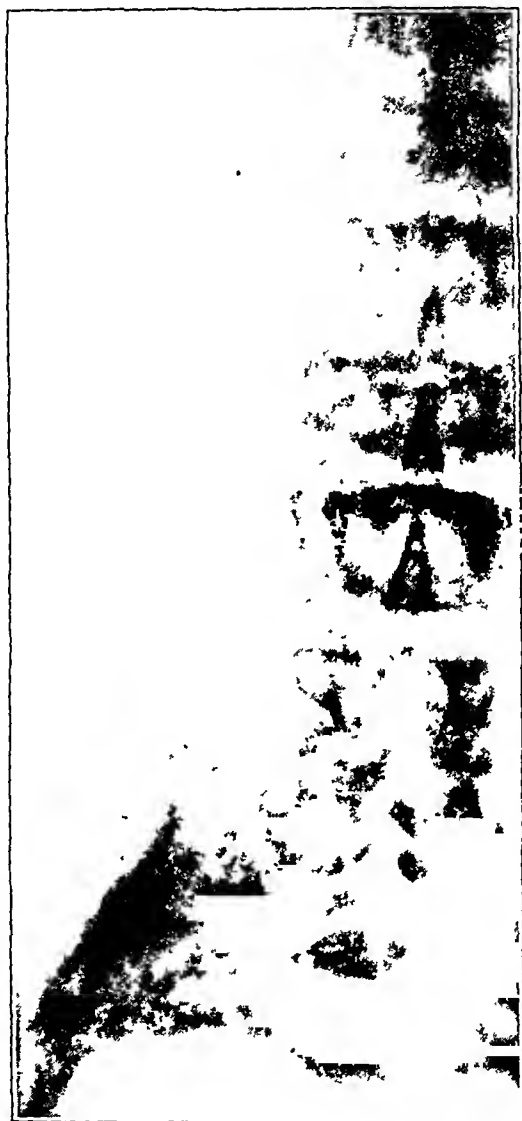


Fig. 5.—Typical cotton-wool appearance of the spine in osteitis deformans.

also to be seen in both forearms. The spine was extensively involved and showed the typical cotton-wool appearance (fig. 5).

CASE 5.—The skull of this patient exhibited definite signs of Paget's disease. No change was visible in the bones of the spine, and there was nothing diagnostic in the upper end of the tibiae. On roentgenographic examination of the skull, there was no doubt as to the diagnosis of Paget's disease. Areas of increased density by the side of patches of decalcification were present. Thickening of the calvarium and lack of differentiation of the tables were evident.

SUMMARY

1. Thirty-four cases of osteitis deformans are described, the age, sex and familial incidence being noted.

2. The mode of onset and the frequency and significance of the pain are described.

3. The types of skeletal changes are recorded, and the factors involved in their production are indicated. Pathologic fractures and sarcomatous changes are noted.

4. Spastic paraplegia is described in two cases, as are also lesser manifestations of neurologic involvement in other cases. It is concluded from present studies and from a review of the literature that neurologic changes in osteitis deformans are usually secondary to bony compression and to arteriosclerosis.

5. Two cases of psychosis are described, and the literature is reviewed. It is concluded that the occurrence of psychosis is no special feature of osteitis deformans but may be due to the concurrent arteriosclerosis.

6. The frequency of arterial degeneration and its occasional complications are observed.

7. Ophthalmologic changes are found to be dependent on bony compression or arterial degeneration. Deafness may be due to compression of the auditory nerve or labyrinth but is more usually associated with disease of the middle ear.

8. The constant occurrence of a high content of plasma phosphatase is observed, and its significance is discussed. The blood calcium and inorganic phosphates are found to approximate normal values.

9. The various etiologic theories are discussed. The syphilitic and neurotrophic theories are found to be without foundation. It is considered that the possible phases of parathyroid activity may be secondary to bony changes of unknown origin. There is insufficient evidence at present to prove that the condition is caused by disturbed function of a ductless gland, inflammation or a possible combination of these two factors.

10. The roentgenographic features of osteitis deformans are described.

PHYSICAL SIGNS AND ROENTGENOGRAPHIC FINDINGS IN LOBAR PNEUMONIA IN ADULTS

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CHICAGO

The physical findings in lobar pneumonia are as familiar to clinicians as are the roentgenographic appearances of the lesions to the roentgenologist, but there are few recorded studies relating in any detail these two aspects of the disease. An investigation of this nature involves consistent observation on the part of the clinician and close cooperation with the roentgenologic department in order to obtain satisfactory data. The results of such a systematic study of forty cases of pneumococcus lobar pneumonia are reported in this paper.

This group of cases is obviously too small to justify any statistical treatment of the data. Furthermore, serum therapy was used in most of the type I and type II cases. However, except in those cases in which specific therapy was administered early in the disease, the clinical course was probably little altered in regard to physical signs and roentgenographic findings.

The classification of types of cases in this series with the mortality incidence is shown in table 1.

METHOD OF STUDY

Physical examinations were made once or twice daily, and the results, with other pertinent observations, were recorded on special standard charts. Practically all examinations were carried out by one of three persons familiar with the purpose of the project.¹ At times, necessarily, the thoroughness of the examination was modified by the condition of the patient, particularly in the later stages of the disease. In these few instances sufficient observations were made to detect any gross change from the previous findings. Most of the patients were examined lying in bed, access to the back being obtained by rolling the patient from side to side. This procedure gave, in general, satisfactory results, but in some instances there was sufficient distortion of physical signs to make our observations somewhat inaccurate, in that transmission of physical signs to the unaffected side gave us

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1. Dr. L. T. Coggeshall assisted in making these observations.

false evidence of apparent involvement in new areas. More recently the patients have been supported in a sitting position during the examination. If properly carried out with adequate assistance, the latter procedure rarely causes distress, and one obtains much more accurate observations.

Daily roentgenograms of the chest were made in most of the cases during the febrile period of the illness. Subsequently, roentgenograms were made at irregular intervals, depending on the course of the convalescence. A portable x-ray apparatus was generally used during the active stage of the disease. Except in rare instances the necessary manipulation for obtaining these films caused little inconvenience to the patient. Occasionally, with extremely ill patients under continuous oxygen therapy, the roentgenograms were omitted.

Histories were carefully taken in an attempt to ascertain, within a few hours, the actual onset of symptoms. However, the onset is not always abrupt, and the patients were occasionally unable to give adequate information. In these cases some arbitrary time was set at which the disease seemed definitely established. A sudden chill or onset of fever or a pleuritic pain developing abruptly without definite prodromal symptoms, when given in the history, was taken as the beginning of the illness. Such symptoms do not represent the theoretical inception of the

TABLE 1.—*Classification and Mortality Incidence in Forty Cases of Pneumococcus Lobar Pneumonia*

Type	Serum Therapy	No Serum	Recovery	Deaths
I.....	12	1	12	1
II.....	3	2	5	0
IIa.....	0	7	6	1
III.....	0	6	2	4
IV.....	0	0	6	3
Total.....	15	25	31	9

disease but indicate the generally accepted time of onset. They are sufficiently constant features to serve as a practical base line for calculation of time intervals. All measurements of time, unless otherwise stated, were calculated from such an arbitrarily established base line. Except in the early stage of the disease, when hours from onset are recorded, all time intervals between observations have been estimated to the nearest half day.

Attention has been directed particularly toward (1) the factors involved in early diagnosis; (2) correlation between the appearance of the roentgenogram and the character of the physical signs in all stages of the disease; (3) the evolution of the disease as observed by the roentgenogram, and (4) the occurrence of visceral displacement.

FACTORS IN EARLY DIAGNOSIS

The necessity of early diagnosis has become of paramount importance since the introduction of specific serum therapy. With this in mind, a presumptive diagnosis of lobar pneumonia should be made in any patient with a history of an acute onset of infection with signs or symptoms referable to the pulmonary system. If, in addition, rusty or blood-tinged sputum containing a predominance of pneumococci is present, the diagnosis is practically certain. The latter finding is not always present in the early stage, and consequently one must utilize all other

available evidence. The white cell count is often of distinct value, for most patients, even at the beginning of the infection, have a marked leukocytosis. A few, however, do not show this reaction.

In table 2 are tabulated the various objective findings and pulmonary symptoms seen within thirty hours after onset. The pneumococci were isolated from the sputum, blood culture or fluid obtained by puncture of the lung, and, in many instances, from at least two of these sources. The column under roentgenographic evidence designates merely presence or absence of roentgenographic signs of a pulmonary lesion and not the extent of the pathologic process. The physical signs, which were extremely variable, are recorded without designation of their

TABLE 2.—*Signs and Symptoms in Early Stage of Pneumonia*

	Type of Pneumo- coccus	Time After Onset, Hrs.	Physical Signs	Roentgeno- graphic Evidence	Symptoms	White Blood Cells
G. F.	II	5	None	+	Pleural pain	21,000
A. M.	II	8	Dulness	+	Pleural pain	10,000
E. C.	IV	13	Dulness; bronchial breathing	+	Pleural pain; dyspnea; cough	13,000
R. H.	I	15	None	+	Rusty sputum; cough	22,000
R. O.	I	19	Dulness	0	Pleural pain	34,000
J. A.	I	21	Bronchial breathing	+	Dyspnea	28,000
E. M.	I	21	None	+	Pleural pain; cough	28,000
C. H.	III	22	Dulness; diminished breath sounds	+	Pleural pain; cough	22,000
F. S.	II	23	Dulness; bronchoves- icular breathing	+	Dyspnea	18,000
R. E.	IIa	24	Dulness	+	Pleural pain; bloody sputum	23,000
L. P.	IIa	24	Dulness; bronchial breathing	+	Rusty sputum	28,000
G. H.	I	25	Dulness; diminished breath sounds	+	Cough; dyspnea; rusty sputum	13,400
H. C.	III	29	Dulness; bronchial breathing	+	Pleural pain	6,400
A. L.	I	30	Dulness	+	None	28,000

intensity or extent. In several instances the signs were so minimal that they would easily have been discounted if lobar pneumonia had not been strongly suspected. As will be pointed out later, the degree of intensity of the physical signs, at this stage, often gave no indication of the extent of the lesion as disclosed in the roentgenogram.

In all cases there were sufficient signs or symptoms relating to the pulmonary system to warrant a presumptive diagnosis of lobar pneumonia. About one fourth of these patients had sputum containing pneumococci when first seen. The leukocytosis was generally definite. One patient, A. M._{II}, however, who went through a severe illness despite early serum therapy, never had a white cell count above 13,000. E. C._{IV}, who exhibited a very mild disease, did not exceed the initial count. G. H._I had a white cell count of 34,000 in the second twenty-four hours. H. C._{III}, with an initial count of 6,400, was at the peak of the disease at

twenty-nine hours with full consolidation of the left lower lobe and partial consolidation of the right lower lobe, and resolution began at three days. The highest count was 10,000 during this time.

Physical signs in the early stage were variable. Detectable dulness was present in ten of the fourteen patients, though in several this was extremely slight. Diminished or increased intensity of breath sounds, with or without râles, occurred less often than dulness, namely, in six of the fourteen cases. In the early period the physical signs rarely involve the area of a whole lobe, so from the point of view of diagnosis they serve only to localize the infectious process in the chest as do the symptoms of pleurisy, cough, sputum or dyspnea.

In hospitals the roentgenogram affords considerable aid in early diagnosis, as is well illustrated in table 2. Of this series, only one patient, R. O.₁, first seen nineteen hours after the initial symptoms, failed to show any shadow in the roentgenogram. However, the character of the onset of the disease, the leukocytosis, pleuritic pain and dulness, which were quite definite, sufficed to warrant a presumptive diagnosis of early lobar pneumonia. Later, the classic signs of consolidation of the entire lower right lobe developed, but the roentgenograms never showed more than faint graying in this region, even though the films were technically satisfactory.

Twenty of the forty patients were first seen forty-eight hours or less after the beginning of the disease. None of those examined after twenty-four hours failed to show a definite lesion in the roentgenograms, although even at this stage physical signs were occasionally absent or minimal, and difficult to detect. One should question seriously a diagnosis of lobar pneumonia in any case in which it is suspected, which, forty-eight hours after onset, fails to show some lesion in the roentgenogram. Only one patient in the series (R. B._{IIa}, table 4) afforded a possible exception to the foregoing statement. This patient was first seen four and one-half days after the initial symptoms of a sudden chill and temperature. Rusty sputum had appeared the day before entry to the hospital. There were no signs suggesting consolidation at the first examination, but crepitant râles were heard throughout the region of the entire lower right lobe. The roentgenogram at that time showed only increased markings in the upper portion of the lower right lobe. Subsequently, signs of consolidation developed over the entire posterior portion of the chest except at the extreme apex and base, with increased density in the same area, as shown by the roentgenogram. It would seem that a diagnosis of lobar pneumonia on the basis of roentgenographic or physical signs would have been difficult in the first forty-eight hours.

COMPARISON OF PHYSICAL SIGNS OF CONSOLIDATION AND
ROENTGENOGRAPHIC APPEARANCE OF THE LESION
AT VARIOUS STAGES OF THE DISEASE

The Developing Lesion.—Until the consolidation reached its maximum, the roentgenogram was found to be much more accurate than the physical signs in disclosing the extent and character of the lesion. The almost invariable presence of an abnormal density in the roentgenogram within twenty-four or forty-eight hours after onset has been pointed out. Comparable manifestations of the lesion as indicated by physical signs occurred less consistently during this early period. Although

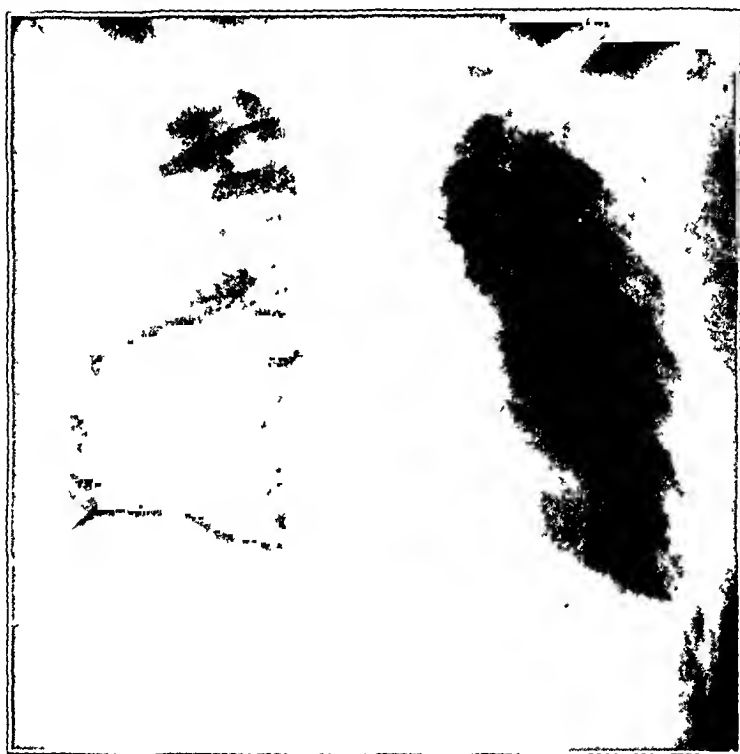


Fig. 1 (E. M.₁).—Roentgenogram taken twenty-one hours after onset. No abnormal physical signs were detected. Note that elevation of the diaphragm was present at this early stage.

physical signs of consolidation were generally present, they tended to be quite minimal and rarely indicated as extensive a lesion as was shown by the roentgenogram.

This is illustrated by the roentgenograms (figs. 1 to 4) of the following patients observed within the first twenty-four hours after the onset of the disease (see tables 2 and 3 for other data).

In E. M.₁ (fig. 1) there was the most striking divergence between the degree and the extent of roentgenographic density and physical signs. This obvious lesion in the upper right lobe gave no definite physical signs of consolidation over the involved area. In R. H.₁ (fig. 2)

no abnormal physical signs were detected until fifty-seven hours after the onset of the disease, when the lesion in the roentgenogram was quite marked. Physical examination of G. F._{II} (fig. 3) disclosed no evidence of consolidation. The lesion in F. S._{II} (fig. 4), which gave a conclusive roentgenographic shadow, caused such meager physical signs that their significance was in doubt until the roentgenogram was seen.

In contrast to these findings, there were three cases in which the evidence of consolidation by physical signs was much more pronounced than in the roentgenogram. In these cases only a faint graying of the affected area of the lung was seen in the daily roentgenograms, although the physical signs were those of frank consolidation. This lack of characteristic density could not be attributed entirely to faulty roentgeno-



Fig. 2 (R. H._I).—*A*, roentgenogram taken fifteen hours after onset. A beginning lesion is seen along the right border of the heart. There were no physical signs of consolidation. *B*, appearance thirty-eight hours after onset. No physical signs of consolidation were detected.

grams, because the findings were consistent throughout the individual series despite variations in the technic of exposure.

Time of Maximum Consolidation.—By the time a lesion had progressed to its maximum consolidation, the divergence between the roentgenographic and the physical signs was no longer so apparent. In most cases the consolidation, when fully developed, was equally well demonstrated by either method.

In tables 3 and 4, the time of maximum consolidation, onset of resolution and rate of clearing, as disclosed by the two methods of examination, are tabulated. The time of maximum consolidation has been taken as the interval between the onset of the disease and the point of time at which the greatest intensity and extent of physical signs or roentgeno-



Fig 3 (G. F. II).—Roentgenogram taken five hours after onset. No physical signs of consolidation were detected.



Fig. 4 (F. S. II).—Roentgenogram taken twenty-three hours after onset. A small area of slight dulness and faint bronchovesicular breathing were detected at the inferior angle of the right scapula.

graphic density were found. Maximum extent of the lesion as shown by roentgenographic or physical examination does not necessarily correspond to the time of maximum intensity of density in the roentgenograms or of signs of consolidation. For example, it was often noticed

TABLE 3.—*Data on Patients Treated with Serum Who Recovered*

	Type of Pneumococcus	Time of Maximum Consolidation		Day of Onset of Resolution		Day of Crisis or Lysis	Time of Beginning Serum Treatment	Duration of Resolution in Days*		Lobes Involved
		X-Ray	P. E.	X-Ray	P. E.			X-Ray	P. E.	
G. F.	II	5 hrs.	33 hrs.	5	2	2-4	13 hrs.	8	3	One†
F. S.	II	23 hrs.	23 hrs.	3½	2½	2	25 hrs.	9+†	8	One†
E. M.	I	21 hrs.	22 hrs.	4½	3½	2	23 hrs.	7	7	One
R. H.	I	2½ days	3½ days	5½	5½	4-6	36 hrs.	..	17	One
G. H.	I	3 days	3 days	5	9	3	48 hrs.	12	7	One
J. A.	I	3½ days	3½ days	5½	5½	4	40 hrs.	13	13+	One
A. M.	I	3½ days	4½ days	6½	6½	7	72 hrs.	2	20+	One
M. T.	I	3 days	3 days	6	6	4-6	48 hrs.	30	30	One
R. O.	I	3 days	4 days	6	6	4-6	36 hrs.	..	17	One
J. L.	I	3½ days	3½ days	4½	4½	7	67 hrs.	41+	33+	Two§
A. M.	II	3 days	3 days	6	5	5	36 hrs.	6+	18+	Two§
M. E.	I	6 days	6 days	7	7	6	6 days	15	..	Two
McC.	I	6 days	6 days	9	9	8-12	6 days	77	77+	Two

* From onset of resolution to the time of disappearance of the lesion.

† Remnants of physical signs or roentgenographic density still remaining at the last examination. (See text.)

‡ Considerably less than one lobe involved.

§ More than one but less than two lobes involved.

X-Ray and P. E. indicate roentgenographic and physical examination, respectively, in this and the following table.

TABLE 4.—*Data on Untreated Patients Who Recovered*

	Type of Pneumococcus	Time of Maximum Consolidation		Day of Onset of Resolution		Day of Crisis or Lysis	Duration of Resolution in Days*		Lobes Involved
		X-Ray	P. E.	X-Ray	P. E.		X-Ray	P. E.	
L. P.	IIa	1 day	1½ days	3	4	2-6	7+†	2	One
E. C.	IV	30 hrs.	30 hrs.	2½	2½	2-6	6+	8+	One
B. G.	IIa	3 days	3 days	6	6	5	8+	8+	One
M. K.	IV	2 days	4 days	6	6	4-14	..	10	One
F. V.	IV	4 days	4½ days	7	6	8-10	18	18	One
L. B.	IIa	5 days	5 days	8	8	7	..	14+	One
A. C.	III	6 days	6 days	7	7	4-6	12	12	One
A. L.	I	6 days	5 days	7	7	5	20	15+	One
R. B.	IIa	6 days	6 days	7	7	8	10+	8	One
F. T.	IV	13	12	7	26	35+	One
H. C.	III	29 hrs.	29 hrs.	3	3	3-9	11+	16+	Two‡
M. R.	IIa	6 days	7 days	8	8	5-7	13+	15	Two‡
K. H.	III	4 days	5 days	7	7	7	12	12	Two
M. M.	II	10	10	8-10	8+	8+	Two
R. E.	IIa	6 days	6 days	8	8	7	11+	8	Three
W. S.	IV	5 days	6 days	6	7	7-12	15+	15+	Three

* From onset of resolution to the time of disappearance of the lesion.

† Remnants of physical signs or roentgenographic density still remaining at the last examination. (See text.)

‡ More than one but less than two lobes involved.

in pneumonia of one lobe that the entire lobe would be involved within forty-eight hours, but the maximum intensity of the physical signs or of the roentgenographic density would not be apparent until twenty-four hours later. Hence the time of maximum consolidation in such a case would be recorded as three days.

On the basis of tabulating the time of maximum consolidation, there is noted in tables 3 and 4 significant uniformity between the development of maximum physical signs and the roentgenographic density. Up to this point the extent and intensity of physical signs were usually considerably in arrears of the apparent involvement in the roentgenogram. Maximum physical signs occasionally did not appear until after maximum density, as shown by the roentgenogram developed, and the opposite situation was also noted. Usually, however, there was a fairly close uniformity in this stage of the disease as detected by these two methods of examination.

We found that of the several signs of consolidation, dullness to percussion usually gave the most accurate evidence of the extent of the lesion as compared with that shown in the roentgenogram. Bronchial breathing or bronchophony frequently conformed to the extent of the area of dullness, but much less often exceeded it than fell short of it.

Onset of Resolution.—Diminution in extent or intensity of physical signs or roentgenographic density was employed as the criterion of beginning resolution. It is seen in tables 3 and 4 that there was a remarkably close correspondence between roentgenographic and physical examination in indicating the inception of this stage of the disease. Roentgenographic evidence of resolution occasionally preceded, and in a few instances followed the physical signs denoting clearing of the lesion. In the majority of cases this stage of the disease was recognized equally well by either method of examination.²

EVOLUTION OF THE DISEASE AS DISCLOSED BY ROENTGENOGRAMS

Sites of Foci of the Pneumonic Lesion.—The original focus of infection, as well as the foci of later areas of involvement, was observed in various areas of the nonstereoscopic pulmonic field. Most of the original foci appeared near the region of the hilus. In figures 4 and 5 the lesions occupied more central portions of the lobe. The focus of spread in the right side of the chest in figure 5 presented an unusual appearance and, because of its sharply circumscribed borders, resembled a carcinomatous metastasis. This lesion subsequently spread laterally and, at the height of its development, was a triangular area of density with its apex at the hilus and its base at the periphery. Figure 6 shows the pneumonic process originating in the peripheral portion of the lung and spreading toward the hilus.

2. Occasionally one can predict the beginning of resolution by physical signs before the criterion mentioned is established, by the advent of coarse, moist râles over the consolidated area. However, this is not an entirely dependable sign, for it does not occur with regularity and may appear without definite relation to resolution.



Fig. 5 (R. E. 11a).—Roentgenogram taken three days after onset. No abnormal physical signs were found in the region of the lesion in the right side of the chest.

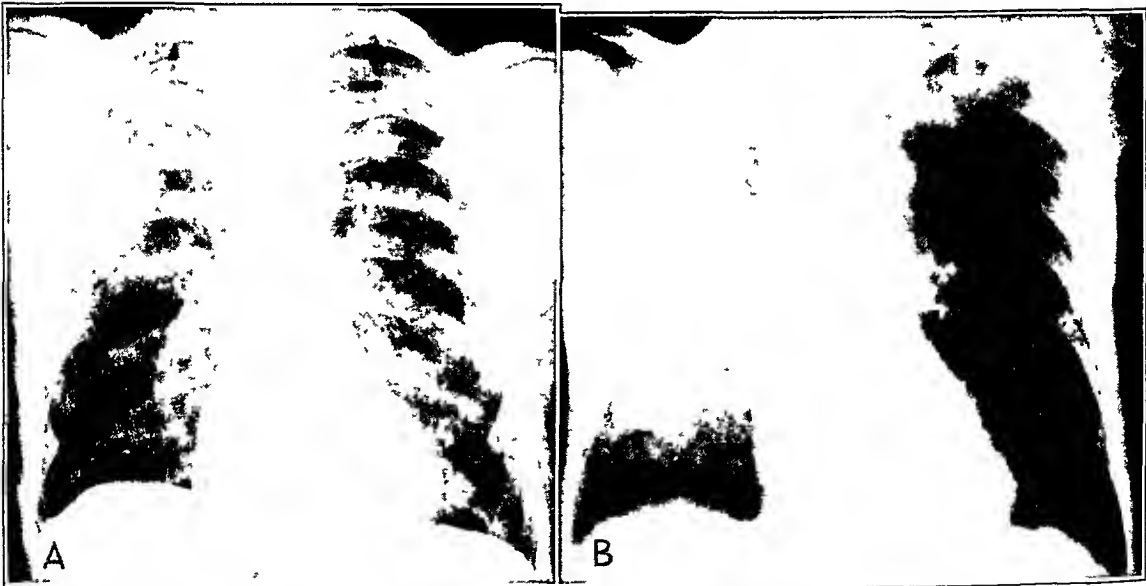


Fig. 6 (McC. 1).—*A*, roentgenogram taken thirty-six hours after onset. Physical examination was not made at this time. *B*, appearance six days after onset. Classic signs of consolidation were present over the upper third of the anterior right side of the chest and the upper two thirds of the posterior right side of the chest.

Rate of Development of Consolidation.—It is often stated that the maximum consolidation occurs in lobar pneumonia at about forty-eight hours. Our findings as summarized in tables 3 and 4 did not confirm this opinion. The cases have been listed in sequence according to the amount of pulmonary tissue involved at the height of the disease. Of necessity, this was an estimation, because frequently it was impossible to be certain that entire lobes, or exactly which lobes, were involved, particularly in the right side of the chest. The classification is sufficiently accurate, at least, to show the lack of uniformity in the rate of consolidation. This variation occurred quite independently of the type of pneumococcus producing the disease.

It is apparent from the data presented that the time required for maximum involvement of either a single lobe or several lobes as detected by either roentgenographic or physical signs was, in the majority of instances, three days or more. In six of the twenty-seven tabulated cases maximum consolidation occurred in thirty hours or less. Serum treatment was given in three of these cases. In two patients, G. F._{II} and F. S._{II} (table 3 and figs. 3 and 4), the pneumonic process was apparently arrested and did not involve a whole lobe. In the three untreated patients in this group, the most rapid maximum involvement of an entire lobe occurred within twenty-four hours (L.P._{IIa}, table 4). H. C._{III} (table 4) showed involvement of one lower lobe and a small area of consolidation in the other lower lobe twenty-nine hours after the onset of the disease. With the exception of these six cases and one other which reached the height of the disease within forty-eight hours, maximum consolidation did not occur until three days or more after the onset of the disease. With multilobed lesions, the day of maximum involvement generally appeared later than when only a single lobe was affected, since the process usually spread from one lobe to another.

Rate of Resolution.—The rate of resolution was likewise found to vary greatly. The figures given on the rate of disappearance of the lesion (tables 3 and 4) were calculated from the day of beginning resolution, as determined by the roentgenogram and by physical examination, respectively, to the time of disappearance of evidence of consolidation. Restitution to normal, roentgenologically, was taken as the time at which there was no remaining evidence of consolidation, although usually accentuation of the bronchovascular markings persisted in the previously affected areas. If any abnormal physical signs or roentgenographic density, however slight, was present on the last examination, a plus sign was used to designate its persistence. The data on the duration of resolution are incomplete in the series, because many of the patients were discharged from the hospital before the lesion had entirely cleared. Furthermore, roentgenograms were taken less frequently during this

stage. In some instances small pleural effusions appeared during convalescence and obscured the roentgenogram as well as disturbed the physical signs of consolidation.

A rough analysis of the data shows that in seven of the cases physical signs of consolidation disappeared about the same time as the roentgenographic evidence. In four cases the roentgenograms appeared to be normal before the signs had receded, and in six instances the reverse situation was noted. In the rest of the cases no adequate comparison could be made because of incomplete observations.

It is shown by the data, presented in tables 3 and 4, that the rate of resolution was quite variable. Weeks or months may be required.

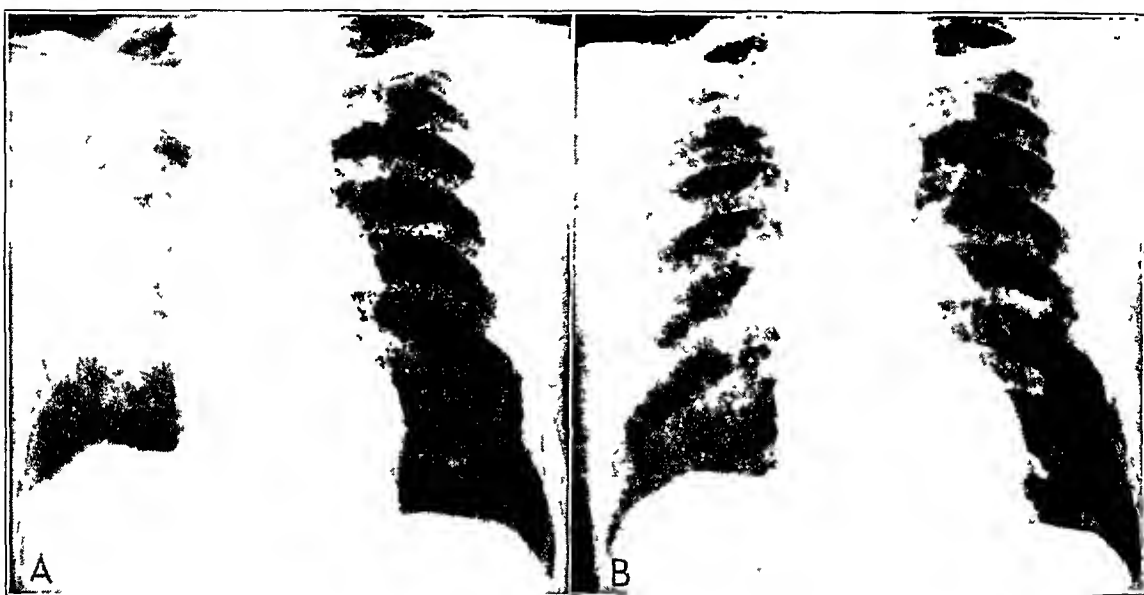


Fig. 7 (McC.₁).—*A*, roentgenogram taken twenty-nine days after the onset of the disease, twenty days after beginning resolution. Physical signs of consolidation were decreasing slowly. Note the deviation of the trachea and elevation of the right side of the diaphragm. *B*, appearance eighty-five days after onset and seventy-six days after beginning resolution. Slight dulness was present over the right scapular area. The roentgenographic appearance is now practically normal.

One patient, McC₁ (table 3, figs. 6 and 7), was observed for seventy-seven days throughout a period of exceedingly slow resolution. The last roentgenogram (fig. 7 *B*) showed a practically normal appearance, though the film taken thirty-eight days before this was far from normal. Some dulness still remained at the time of the last examination.

In this series there was no uniformity in persistence of any particular sign of consolidation. Dulness was less likely to remain than some alteration in the transmission of voice or breath sound. Increased whispered voice was often the last abnormal sign to disappear.

Sante³ stated that resolution, as shown by the roentgenogram, should be complete in two weeks in any normal convalescence. It is probably true that most cases have practically cleared up at this time, but many have not, and resolution continues at a slower rate with eventual complete recovery.

Sequence of Resolution.—It was found impossible to make a definite statement in regard to the sequence of clearing of a single lobe. Whereas spread in one lobe occurred generally as an even uniform involvement, the clearing process took place in a distinctly patchy manner. It was practically impossible to detect any distinct difference in the rate of resolution of any one portion of the lobe, except that the hilar densities in general subsided more slowly than the main peripheral areas.

In cases showing involvement of more than one lobe, several types of resolution were observed. In several instances of multilobed involvement in which the focus of spread had not advanced to complete involvement of an entire lobe, the later area of infiltration cleared more rapidly than the older process. This may be more apparent than real because of the lesser amount of tissue involved in the later focus. In other cases, however, in which two or more lobes were involved in sequence with several days' difference in the time of maximum consolidation, the signs of beginning resolution appeared in all areas simultaneously. In some instances the first lobe involved gave the first evidence of clearing. Two cases with lesions of multiple lobes showed resolution proceeding in the earliest area of involvement, while actual spread was taking place into new foci. In one of these cases the pneumonia was a type IV; in the other, a type II. Roentgenograms of one of these patients, K. V._{IV}, are shown in figure 8. The original lesion began in the lower right lobe, then gradually spread upward until the entire right lung had been consolidated. Before this process was completed, resolution had taken place in the area first infected.

Unfortunately, there were too few cases in the series suitable for adequate study of these phenomena of resolution to make possible any statement as to the factors concerned. Usually resolution appeared first in the older lesion, although in certain instances the more recently involved areas began to clear simultaneously or even before the older lesion. Our knowledge of the mechanisms of resolution is inadequate to explain these different types of reaction.

OCCURRENCE OF VISCERAL DISPLACEMENT

Elevation of the Diaphragm.—In twenty-nine of the forty cases here reported the diaphragm was well visualized in the roentgenogram at some time during the active stage of the disease. In eighteen cases

3. Sante, L. R.: The Chest, Ann. Roentgenol. **11**:203, 1930.

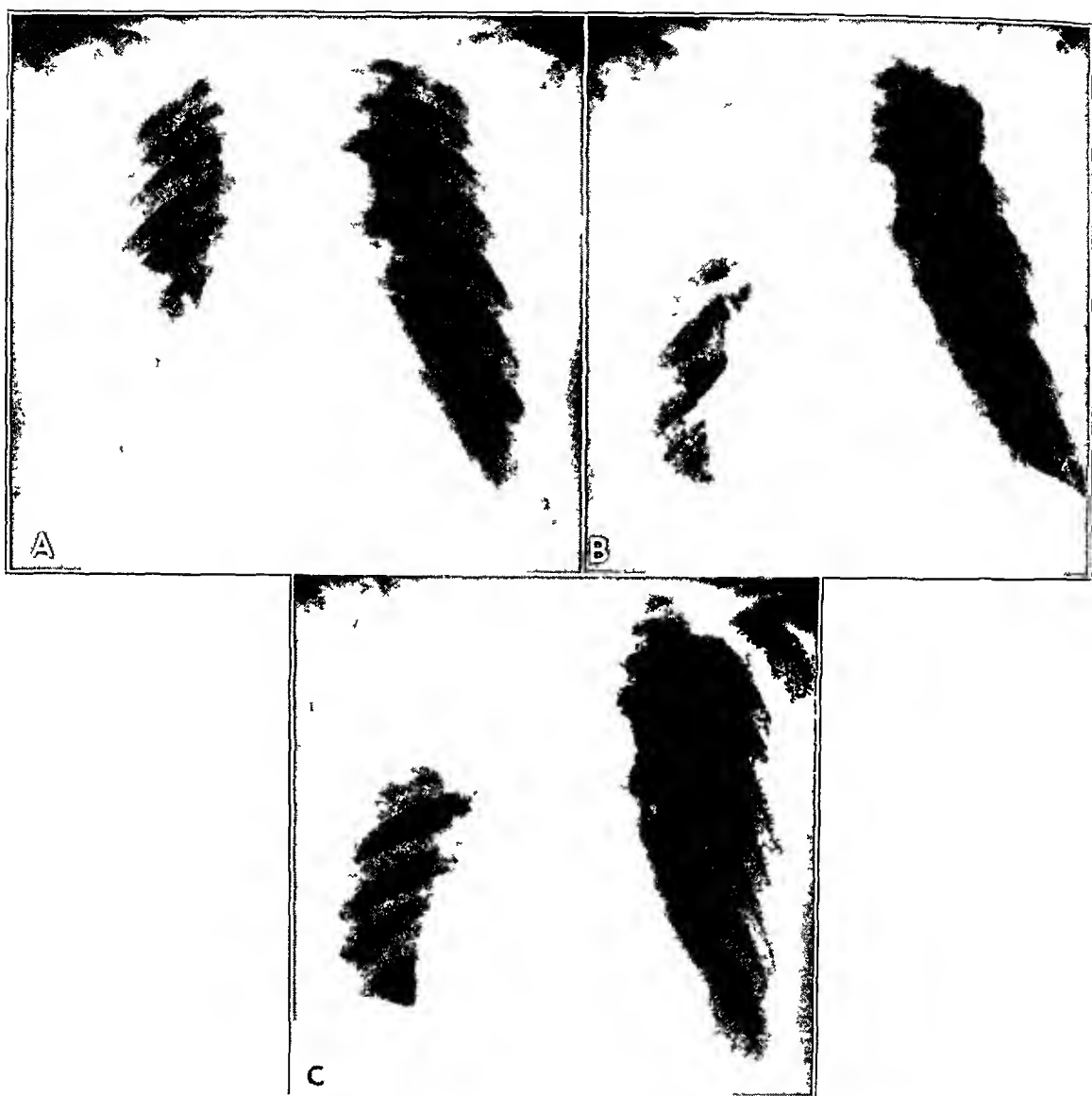


Fig 8 (K. V._{IV}).—*A*, roentgenogram taken five days after onset. The first roentgenogram taken three days after onset showed maximum density near the cardiac shadow. Some clearing in this region is already apparent. There was no evidence of resolution by physical examination. *B*, appearance seven days after onset. The lesion is spreading upward while clearing progresses in the lower areas. The physical signs of consolidation have extended upward. There was an increase in moist râles at the base of the right lung at this time, suggesting resolution. *C*, appearance eight days after onset. Further spread and resolution have occurred. The physical signs of consolidation had greatly diminished at the base and had spread upward to include the apex.

there was definite elevation of the leaf of the diaphragm on the affected side. Eleven did not show this change, but in most of these cases the outline of the diaphragm was obliterated by a small amount of fluid or by dense consolidation, so that one cannot state whether or not there was elevation later in the disease.

Several of the cases in this series were studied with the double exposure technic described by Jung and Van Allen,⁴ in which the film is exposed at both maximum inspiration and maximum expiration. By this technic the maximum excursion of the two sides of the diaphragm may thus be compared in the same film. These cases were reported in a separate paper.⁵ All of them showed elevation or diminished excursion of the diaphragm on the affected side. In one case in this group a roentgenogram made during deep inspiration with the usual technic failed to show elevation of the diaphragm, but with the double exposure technic the roentgenogram showed definite diminution in the extent of the excursion of the diaphragm on the side of the lesion. It would appear from this observation that alteration in the relationship of the two sides of the diaphragm in some instances would not be apparent in the films taken at the moment of maximum inspiration.

All grades of elevation of the diaphragm from slight to marked were noted in the series. Elevation was rarely detected by physical signs. In certain instances the diaphragm resumed its normal position within a few days after resolution began, but in others the elevation persisted even after the lesion had apparently resolved.

Displacement of the Mediastinum.—Displacement of the mediastinal structures was not a prominent feature in the roentgenographic findings in this series. Detection of slight changes in the position of the mediastinum was rendered difficult because many of the films were made with a portable x-ray machine at the bedside, with the result that often the sagittal plane of the chest was not perpendicular.⁶

However, taking this factor into consideration, there were three cases in which there was slight but definite displacement of the mediastinum toward the affected side during the acute stage of the disease. In one other case, not included in the series of forty, there was marked displacement when the patient was first observed, forty-eight hours after onset. This case, in contrast to the other three, presented the classic

4. Jung, T. S., and Van Allen, C. M.: A Method of Recording Respiratory Movements in a Single Roentgenogram, *Nat. M. J. China* **17**:194, 1931.

5. Wu, Ching: Visceral Displacement in Pneumonia, *Radiology* **19**:215, 1932.

6. The ideal roentgenologic examination for demonstration of this phenomenon would consist of stereoscopic films and fluoroscopic observation. Facilities for stereoscopic filming of bedridden patients are now available and will be reported presently by others. They had not been developed at the time this work was done.

signs of atelectasis⁷ and a degree of mediastinal shift seen in cases of "massive collapse." There were diminished to absent breath sounds over the entire left anterior portion of the chest and frank signs of consolidation at the base posteriorly. The displacement of the heart to the left was detected by physical examination and was clearly seen in the roentgenogram. After twenty-four hours the signs had changed markedly. The heart had returned to almost normal position, and there was good aeration of the anterior portion of the chest. Posteriorly, the signs of consolidation had greatly diminished. Unfortunately this patient had a moderately enlarged heart which obscured part of the lower left portion of the chest, so that no good evidence of consolidation was seen in the roentgenogram, though the physical signs were quite definite. Atypical type II pneumococci were recovered from the sputum. Although there was undoubtedly true collapse present, as well as some pneumonic lesion, we are not warranted in submitting this case as a typical example of lobar pneumonia. One must say, however, that collapse of the lung of this type may occur in rare instances of pneumococcus pneumonia.

In four cases there was definite displacement of the mediastinal structures during the stage of resolution. The most striking patient in the entire series was McC.¹ (figs. 6 and 7, table 4), who was observed throughout a period of protracted resolution. Figure 6 *A* shows a lesion which began at the periphery and reached its maximum development six days (fig. 6 *B*) after the onset of the disease. By this time there was slight displacement of the trachea toward the lesion. Resolution began on the ninth day. Figure 7 *A* was made twenty-nine days after onset, or twenty days after resolution began. At this time maximum visceral displacement was apparent. Also, there was marked diminution in the area of the right pulmonic field in comparison with that of the left pulmonic field. The difference in the two sides was probably the result of diminished expansion of the right lung, combined with compensatory emphysema of the left lung. Figure 7 *B*, made eighty-six days after the onset of the disease and seventy-seven days after resolution began, shows almost complete restitution to normal. The diaphragm was still slightly elevated, but the trachea had resumed its normal position, and there had been a considerable increase in the area of the right pulmonic field. There were still some abnormal physical signs present, but these were very slight. This was our last observation on this patient. At no time were there any of the usual physical signs of atelectasis.

7. The term "atelectasis" is used here in the sense of "airlessness" due to collapse of the lung.

COMMENT

The data presented in this paper are part of a systematic attempt to correlate certain clinical, immunologic, bacteriologic and pathologic features of pneumococcus pneumonia. Even in this small series the extreme variability of the reaction of individual hosts to the same type of pneumococcus was apparent. The classic picture may result from infection with any type. Pneumonia due to the group IV pneumococcus seemed to present the greatest variation; the disease caused by types I and II, the least. In the studies on experimental pneumonia in dogs reported by Terrell, Robertson and Coggeshall,⁸ in which dosage and type were controlled, this same variability was apparent.

We attempted to correlate the degree of leukocytosis with the intensity of the roentgenographic shadow and the severity of the disease. In this respect, also, there was great divergence of findings. There were instances of marked density with relatively low white blood cell counts as well as the opposite situation. In general, of course, the severe cases had the more marked leukocytosis, but the degree of white cell reaction certainly showed no constant relation to the type of pneumococcus causing the disease. Likewise, the febrile reaction of the patient showed no consistent relationship to the type of pneumococcus.

From a study of the data in tables 3 and 4, one is impressed with the considerable variability in the time relationship of resolution to crisis. The onset of resolution may precede, occur simultaneously with, or follow crisis. Usually it follows crisis. Furthermore, resolution may be proceeding in one area while spread into other regions is occurring and the toxic symptoms of the disease are persisting. Thus the abrupt and the more prolonged fall of temperature with the concomitant decrease of toxic symptoms, which are called crisis and lysis, respectively, are not directly related to the phenomena of resolution, as Cole has pointed out.⁹

A point of practical interest brought out by this study was the assistance which may be derived from the roentgenogram in early diagnosis. In a number of instances the appearance of the roentgenogram substantiated the presumptive diagnosis, so that serum therapy was started before a definite etiologic diagnosis was made. It would be incorrect to say in general that the appearance of density in the roentgenogram in the early stage is "characteristic" of lobar pneumonia except in consideration of the history. The rapid development of the density, when its probable age is known, and its visual localization to

8. Terrell, E. E.; Robertson, O. H., and Coggeshall, L. T.: *Experimental Pneumococcus Lobar Pneumonia in the Dog: I. Method of Production and Course of the Disease*, J. Clin. Investigation **12**:393, 1933.

9. Cole, Rufus: *Acute Lobar Pneumonia*, in *Nelson Loose-Leaf Medicine*, New York, T. Nelson & Sons, 1920, vol. 1, p. 228.

a single focus in any one lobe serve to differentiate it from most other acute pulmonary infections.

Likewise, as has been frequently pointed out by roentgenologists, the resolving lesion may present many bizarre features. Characteristically the clearing lesion gives a patchy shadow in contrast to the even density of a developing lesion, but at times it may simulate perfectly single or multiple abscesses of the lung, or more often widespread tuberculous lesions. In a single film one could certainly not dismiss either diagnosis. Rarely, however, does such an appearance persist sufficiently long to confuse the diagnosis. A large, apparent abscess with thick capsule will disappear in several days, and, similarly, the supposed tuberculous lesion will melt away rapidly.

There is considerable confusion in the literature concerning the locus of origin of the lesion in lobar pneumonia as detected in the roentgenogram. Most writers tend to stress the relationship to the hilus. Though this perhaps is the most frequent site of the original focus, as disclosed by the nonstereoscopic roentgenogram, the lesion may occur in other areas of the pulmonic field. There are naturally few observations made on the site of the initial focus besides those made by roentgenograms. Figures 4 and 5, shown here as examples of central foci apparently not originating from the hilus or related to the lateral periphery, admittedly do not offer conclusive evidence of separation from the pleural surfaces. Undoubted evidence of a central focus unrelated to the surface of the lung or to the hilus can be obtained only at autopsy. Assmann¹⁰ reported a case in which spread occurred from the upper right lobe to the central portion of the left lung. The latter lesion was only disclosed in a roentgenogram of the lungs after death and was corroborated by the findings at autopsy. As Mason¹¹ stated, no conclusive evidence has so far been produced to show that the pneumococcic lesion may occur in the center of a lobe remote from the pleural surfaces. Only by autopsy will this point be settled. The case mentioned by Assmann¹⁰ was not reported in detail, and from his statements one cannot be certain that the lesion did not have any connection with the interlobar pleural surfaces.

The peripheral origin of a pneumonic lesion is not infrequently observed. Two examples occurred in this series; one was the original focus, and the other, the site of a later area of spread. Mason¹¹ made the same observation in children. In experimental lobar pneumonia in dogs, Terrell, Robertson and Coggeshall⁸ produced the initial lesion by implantation of pneumococci in the periphery of the lung. Blake and

10. Assmann, Hubert: *Klinische Röntgendiagnostik der inneren Erkrankungen*, ed. 4, Leipzig, F. C. W. Vogel, 1929, p. 265.

11. Mason, H. H.: Lobar Pneumonia in Childhood, *Am. J. Dis. Child.* **11**:188 (March) 1916.

Cecil,¹² with a different technic, localized the initial focus in the hilar region of monkeys.

We have been particularly interested in studying these cases in attempting to detect evidence of atelectasis or collapse in lobar pneumonia. Coryllos and Birnbaum¹³ believe this to be an essential feature in the disease. Except in one instance described in detail, we failed to detect evidence of true atelectasis in any case. This case, as was stated, could not be classed by any criteria as a typical lobar pneumonia. Of the cases seen early in the disease, i. e., within thirty hours of onset, none gave any evidence of this condition. Shift of the mediastinum does occur, but in no case in this series did it approach the degree found in massive atelectasis as diagnosed by clinical or roentgenographic signs. One must acknowledge, however, that the clinical diagnosis of this condition can be made only when considerable collapse is present. 'Pneumonia in children and the experimental disease in dogs unquestionably show this displacement of the mediastinum clearly in a much higher percentage of cases.' However, it does not follow that the displacement is due primarily to actual collapse of a portion of the lung, though to some degree this may be a factor. The observations of Robertson, Coggeshall and Terrell¹⁴ on the pathologic changes in experimental pneumonia are significant in that they failed to show any evidence of plugging of the bronchi, which is postulated as a necessary precursor to collapse of the lung in cases showing a definite shift of the mediastinum.

We feel that the degree of visceral displacement usually encountered in lobar pneumonia can be adequately accounted for on the basis of the experimental studies of Van Allen and Wu.¹⁵ They demonstrated an increase in the elastic tension of the dog's lung in experimental pneumonia in both the preconsolidative and postconsolidative stages. The increased tension presumably occurs as a result of the thickening of the alveolar and lobular septums which is caused by dilated capillaries and interstitial inflammatory fluids and cells. This results in diminished expansibility of the lung, so that at full inspiration the inflamed tissue fails to expand to its usual volume. During the consolidated stage, the lung is, of course, fixed and neither expands nor contracts with respiratory movements. Under these conditions some adjustment of the pulmonary environs must take place in order to maintain the balance

12. Blake, F. G., and Cecil, R. L.: Studies in Experimental Pneumonia: II. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys, *J. Exper. Med.* **31**:445, 1920.

13. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia, *Arch. Surg.* **18**:190 (Jan.) 1929.

14. Robertson, O. H.; Coggeshall, L. T., and Terrell, E. E.: Experimental Pneumococcus Lobar Pneumonia in the Dog: III. Pathogenesis, *J. Clin. Investigation* **12**:467, 1933.

15. Van Allen, C. M., and Wu, Ching: Increased Elastic Tension of the Lung in Experimental Pneumonia, *J. Clin. Investigation* **11**:589, 1932.

of intrapulmonary pressure. Thus, to compensate for this diminution in, or lack of, expansibility of the pneumonic lung, visceral displacement may occur.

In most cases of pneumonia in adults visceral displacement cannot be demonstrated clinically and may be apparent only in the roentgenograms taken at maximum inspiration. It is usually manifested only by alteration in the excursion or position of the diaphragm. In our studies an unmistakable shift of the mediastinum was an unusual finding. With the development of facilities for fluoroscopy and for obtaining stereoscopic films of patients with pneumonia, it is probable that more adults would show slight degrees of mediastinal shift than we have indisputably demonstrated in this series. Children and dogs both have much more mobile mediastinal structures and consequently more often show definite displacement of the mediastinum.

SUMMARY

Forty cases of pneumococcus lobar pneumonia were studied by means of serial daily roentgenograms and physical examinations. A comparison was made between these two methods of examination at various stages of the disease. The roentgenogram was shown to be superior to physical signs in detecting the early lesion and in disclosing the extent of the process while the consolidation was developing. At the stage of maximum consolidation, however, both methods of examination were, in general, equally informative. Evidence of the onset of resolution as detected by the roentgenogram and by physical signs appeared simultaneously in most cases.

Various phases of the evolution of the disease were studied in the serial roentgenograms. The rate of consolidation of lesions of a single lobe varied from one to six days. Maximum consolidation in the majority of cases did not occur until at least three days after the onset of the disease. The sequence of resolution in areas of consolidation of different ages (i. e., in different lobes) was quite variable. In some instances the first area to consolidate was the first to show resolution; in other cases clearing began concurrently with, or even followed, the later areas of involvement. Two cases showed resolution and spread occurring simultaneously in different areas.

Visceral displacement as seen in the roentgenogram was generally manifested as an elevation of the diaphragm on the affected side. This occurred in at least eighteen of the twenty-seven cases in which the diaphragm was visualized. In seven cases of the total series a slight shift of the mediastinum toward the lesion was demonstrated, but in no instance was this displacement comparable to that seen in massive collapse of the lung. Mediastinal displacement was not seen in the fourteen cases observed within thirty hours or less after the onset of the disease.

MECHANISM OF PAIN IN GASTRIC AND DUODENAL ULCERS

VII. FURTHER OBSERVATIONS

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The voluminous literature on the mechanism of pain in ulcer has been reviewed and discussed in considerable detail in previous articles. It will suffice here to mention only the more noteworthy contributions. Talma¹ in 1884 reported the production of severe epigastric distress by the injection of 500 cc. of a solution of hydrochloric acid (1:750) into the stomachs of two patients, one with a gastric carcinoma and the other, judging from the history, with a benign peptic ulcer. The distress induced was relieved by magnesium oxide. Suyling² confirmed both of these observations in 1888, and he concluded that hyperesthesia for dilute hydrochloric acid is frequently the cause of gastric pain. Bönninger³ reported in 1909 that the distress of gastric ulcer could be brought on regularly by the introduction into the empty stomach of from 100 to 200 cc. of a tenth-normal solution of hydrochloric acid. In 1912, Sippy⁴ stated that "the pain and discomfort of uncomplicated ulcer are due to the irritative action of hydrochloric acid on the nerves exposed in the ulcer." In 1923, in discussing the essential factors in the production of ulcer pain, Sippy⁵ again declared:

Clinically a high degree of free hydrochloric acid is practically always present. . . . It is practically certain that free hydrochloric acid is the important element in the irritant. At least it is constantly associated with the irritant. Clinically, distress attributed to uncomplicated ulcer is found only when the fluids of the stomach contain free hydrochloric acid in adequate concentration.

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1. Talma: Zur Behandlung von Magenkrankheiten, *Ztschr. f. klin. Med.* 8:407, 1884.

2. Suyling, J. P.: Beitrag zur Kenntnis der Hyperaesthesie für Salzsäure, *Berl. klin. Wchnschr.* 25:869, 1888.

3. Bönninger, M.: Zur Diagnose des Ulcus ventriculi, *Berl. klin. Wchnschr.* 45:396, 1908.

4. Sippy, B. W., quoted by Musser, J. H., and Kelly, T. C.: *Handbook of Practical Treatment*, Philadelphia, W. B. Saunders Company, 1912, vol. 2, p. 349.

5. Sippy, B. W., in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1923, vol. 3, p. 132.

These statements were made on the basis of innumerable aspirations of the stomach during the presence of ulcer distress, although no figures or statistics are recorded. On the other hand, Löwenthal,⁶ Schmidt,⁷ Boring,⁸ Hurst⁹ and Reynolds and McClure¹⁰ had introduced varying amounts of hydrochloric acid into the empty stomach in concentrations of from 0.5 to 2 per cent without producing distress either in normal persons or in patients with ulcer.

In 1926, one of us (W. L. P.¹¹), working on patients with ulcer during periods of rather marked spontaneous distress and therefore with sensitive pain-producing mechanisms, drew the following conclusions with regard to ulcer distress:

1. It may be relieved by emptying the stomach.
2. It may be made to reappear by reinjecting the aspirated gastric content.
3. It is not initiated by introducing into the stomach aspirated gastric content in which the free acidity has been neutralized by alkali.
4. It may be made to reappear by injecting pure solutions of hydrochloric acid of normal and entirely physiologic concentration (0.2 to 0.3 per cent) or by stronger solutions (0.5 per cent).
5. It may be initiated by other chemical irritants such as dilute solutions of sulphuric acid, acetic acid and sodium hydroxide.
6. The distress so produced is relieved by the removal or neutralization of the chemical irritant.
7. The distress is the patient's typical pain both in type and in location, varying in severity from a mild discomfort to excruciating pain. It may or may not be as severe as the patient's usual distress.
8. Such distress is not ordinarily produced by similar injections into the normal stomach or in patients with ulcer during spontaneous or induced remissions.
9. The pain may be initiated by the acid gastric secretion excited by the subcutaneous injection of histamine.

It was also noted that in some normal patients, as well as in patients with ulcer, the acid solutions occasionally produced a mild sensation of

6. Löwenthal, Max: Beiträge zur Diagnostik und Therapie der Magenkrankheiten, Berl. klin. Wchnschr. **29**:1188, 1892.

7. Schmidt, J. E.: Ein Beitrag zur Frage der Magensensibilität, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:278, 1909.

8. Boring, E. G.: The Sensations of the Alimentary Canal, Am. J. Psychol. **26**:48 (Jan.) 1915.

9. Hurst, A. F.: Goulstonian Lectures on the Sensibility of the Alimentary Canal, New York, Oxford University Press, 1911.

10. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1 (Jan.) 1922.

11. (a) Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: II. The Production of Pain by Means of Chemical Irritants, Arch. Int. Med. **38**:694 (Dec.) 1926 (in this article, page 703, line 4 should read, "55 cc. of gastric juice injected"); (b) *ibid.*, p. 700, exper. 393.

epigastric warmth and burning, at times associated with nausea and even severe emesis. These symptoms were recognized by the patients with ulcer as entirely independent of the ulcer syndrome, and were probably due to duodenal irritation.¹²

As a result of these observations, it was concluded that hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer. Kymographic and roentgenologic studies¹³ were undertaken at that time in an effort to determine the manner in which the acid produced the distress. It was found that in the great majority of the patients there was no relationship between ulcer pain and gastric peristalsis, duodenal peristalsis, gastric tone, the condition of the pylorus or that of the duodenal bulb, but that in occasional instances of intermittent, and also of remittent, pain the waves of pain, or the exacerbations in it, corresponded exactly with the peristaltic contractions of the stomach as recorded by the kymograph. These observations confirmed the previous findings of Ginsburg, Tumpowsky and Hamburger,¹⁴ Carlson¹⁵ and Hardt.¹⁶ It was noted that the cases in which gastric peristalsis constituted an adequate stimulus to the pain-producing mechanism were ones with unusually severe pain, and, furthermore, that after the sensitivity of the pain-producing mechanism subsided, gastric peristalsis

12. Palmer, W. L.: The "Acid Test" in Gastric and Duodenal Ulcer; Clinical Value of Experimental Production of Typical Distress, *J. A. M. A.* **88**:1778 (June 4) 1927.

13. Palmer, W. L.: (a) The Mechanism of Pain in Gastric and Duodenal Ulcers: III. The Rôle of Peristalsis and Spasm, *Arch. Int. Med.* **39**:109 (Jan.) 1927. (Some errors occurred in this article which I should like to correct here. Mention of figures 2 and 8 was omitted from the text, and the numbers of all illustrations as given in the text, except figure 1, are therefore incorrectly given. Reference to figure 2 should be inserted in the last line on page 112 following "The fourth tracing"; hence "figure 2" in the seventh line on page 113 should read "figure 3"; "figure 3" in the fourteenth line on the same page should be "figure 4," and so on down to page 117, in the fourteenth line of which "figure 8" should be inserted after the word "tracing." From here on the references to the illustrations should be increased by two; i. e., "figure 4" in the twenty-first line on page 117 should be "figure 6"; "figure 7" in the thirty-seventh line on page 120 should be "figure 9," etc. On page 128, columns 2 and 3 of table 4 should be headed "Acid Test.") (b) *Ibid.*, p. 124; (c) p. 131; (d) p. 116, fig. 7; (e) p. 129.

14. Ginsburg, Harry; Tumpowsky, Isidor, and Hamburger, W. W.: Contributions to the Physiology of the Stomach: XXXV. The Newer Interpretation of Gastric Pain in Chronic Ulcer, *J. A. M. A.* **67**:990 (Sept. 30) 1916.

15. Carlson, A. J.: Contributions to the Physiology of the Stomach: Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, *Am. J. Physiol.* **45**:81 (Dec.) 1917.

16. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum, *J. A. M. A.* **70**:837 (March 23) 1918.

became painless at a time when pain could still be induced by the introduction of acid solutions into the stomach. It was also found that pain could be induced by the injection of acid into the stomach, in spite of preliminary atropinization and that it was not relieved by the intravenous injection of dextrose. The conclusion was reached that under certain conditions gastric peristalsis, as well as hydrochloric acid, constitutes an adequate stimulus to the pain-producing mechanism. Acid sensitization, however, seemed to be an essential prerequisite for the mechanical production of pain. The exact mechanism by which pain was produced by the acid and by gastric peristalsis was not clear. There was reason to think that it arose from the lesion itself, that peristalsis evoked pain as the result of mechanical irritation of the highly sensitive inflamed area, and that the acid likewise acted in some way directly on the ulcer. It was suggested that the mechanism might consist of the production of edema in the tissue about the edge of the ulcer, of localized muscular spasm or of direct irritation of exposed nerve endings.

Since the publication of this work, other investigators have described findings in part confirming and in part disagreeing with it. It seems advisable to analyze these reports in more or less detail. Cobet and Gutzeit,¹⁷ in 1926, found that the injection of small amounts of dilute hydrochloric acid into the stomach produced distress in only two cases. On the other hand, they were unable roentgenologically to correlate ulcer pain with spastic and peristaltic changes in the stomach. Consequently they concluded that their attempts to produce spasm or pain by means of either electrical or chemical (acid) irritation in gastric ulcer had been unsuccessful. Berg,¹⁸ in 1926, was also unable to make out any clear relationship roentgenologically between pain and gastroduodenal spasm or motility.

Hess and Faltitschek,¹⁹ in 1928, in an important communication described almost total gastric spasm without pain in cases of tumor of the brain, Parkinson's disease and multiple sclerosis. The spasm was thought to be of central origin, due to irritation of the vagus. These authors also ascribed the regional gastric spasm described by Assmann²⁰ and others in tabetic crisis to central stimulation of the vagus. The absence of pain in the conditions mentioned was attributed by Hess and Faltitschek to central inhibition of the pain sense, but evidence in sup-

17. Cobet and Gutzeit: Zur Entstehung der Spasmen und Schmerzen beim Magengeschwür, *Deutsches Arch. f. klin. Med.* **150**:295, 1926.

18. Berg, H. H.: Die direkten Röntgensymptome des Ulcus duodeni und ihre klinische Bedeutung, *Ergebn. d. med. Strahlenforsch.* **2**:320, 1926.

19. Hess and Faltitschek: Ueber Gastropasmus bei organischen Nervenleiden, *Wien. klin. Wchnschr.* **41**:1366, 1928.

20. Assmann, Herbert: *Klinische Roentgendiagnostik der inneren Erkrankungen*, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 463.

port of this hypothesis is not presented. Painlessness, lack of muscular rigidity and lack of local hyperesthesia are considered by them to be characteristic of gastric spasm of central origin. No evidence is offered, however, to prove that gastric spasm of peripheral origin is painful.

In the same year, Poulton²¹ advanced the theory that visceral pain is due not to peristalsis, or to peristalsis and ballooning as suggested by Hurst,²² but to stretching with consequent deformity of the nerve endings subserving the sense of pain, situated in the walls of the viscus: ". . . I would support the view that visceral pain is an affair of the whole visceral wall and not of any isolated lesion in it, and that peptic ulcer produces painful effects secondarily by causing reflex increase of tone." The experiments cited in support of this were performed on the esophagus. The evidence offered in the two cases of ulcer described is entirely inadequate, although in one record (fig. 8) some relationship is to be noted between the variations in pain and the variations in intragastric pressure. Poulton disposes of the hypothesis that pain results from the mere contact of the ulcer with acid by the statement that the suggestion is now so generally discredited that he need only mention the fact that pain may be present with peptic ulcer when there is no free acid in the stomach. Proof of this is not offered. The production of pain in some cases by the introduction of acid into the stomach, according to Poulton, is presumably due to an increase in tonus. It was shown by Palmer,¹³ and it may be seen again in the tracings presented in the present paper, that ulcer pain is not dependent on or accompanied by changes in intragastric pressure or gastric tone.

Wilson²³ in 1928, on the basis of roentgenologic observations, concluded that in duodenal ulcer, pain bears no relationship to gastric peristalsis or to the chemical reaction of the gastric content, but is due to a sustained contraction of the duodenal bulb. The act of squeezing the gastric content into the contracted bulb and thereby dilating it relieved the pain in thirteen of sixteen cases. The three protocols cited are not convincing. The maneuver employed is one commonly used in roentgenology and gives only momentary filling of the bulb. Apparently the relief observed by Wilson was also momentary. Another factor to be considered in appraising this work is that the external manual pressure of the palpating hand produces in effect a counter-irritant and possibly relieves the pain momentarily in this manner. Wilson's work is also not

21. Poulton, E. P.: Oliver-Sharpey Lectures on an Experimental Study of Certain Visceral Sensations, *Lancet* **2**:1223 and 1277, 1928.

22. Hurst, A. F.: *Brit. M. J.* **1**:145, 1925.

23. Wilson, M. J.: Duodenal Ulcer: Observations on the Behavior of Stomach and Duodenum in the Presence of Pain, *Arch. Int. Med.* **41**:633 (May) 1928.

in accord with the previous findings of other observers.²⁴ It is interesting in this connection to note that MacLeod²⁵ has attributed duodenal ulcer pain to distention of the duodenal cap with gas, offering as evidence experiments in which pain was caused by injecting air into that portion of the intestine. The production of pain mechanically in this way, however, is quite compatible with observations to be described in this report. Palmer^{13b} showed originally, however, that distention of the bowel at a point distal to the ulcer might produce pain indistinguishable to the patient from typical ulcer distress.

Hardy²⁶ studied the problem of pain in 1929, using a modified "acid test"¹² and took exception to the conclusion that acid is the normal stimulus for the pain-producing mechanism. His reasons were, in part, the following:

The pain is rarely severe and the patient, though able to identify it, will often volunteer the information that it is not nearly as severe as his typical distress, and this, be it noted, in the presence of acid values far in excess of those ever present in health or disease. The pain rarely shows itself when the acid concentration is at its maximum, that is, immediately after its introduction.

It is true that the pain is frequently not as severe as the spontaneous distress, but, on the other hand, it is not at all uncommon in our experience for the patient to writhe in agony and to give every manifestation of a person in severe pain. Hardy's results may be due in part to his modification of the test; he emptied the stomach at the end of each thirty minutes before the further injections of the acid. Still more important, in our opinion, is Hardy's failure to give adequate consideration to the factor of *time*. Pain seems to be the product of at least three factors: the sensitivity of the lesion, the concentration of the acid and the length of time the acid is in contact with the lesion. If the sensitivity is great, the concentration of acid required is lower and the interval of time shorter. Conversely with less sensitive ulcers, the requisite concentration of acid and interval of time are greater. Indeed the interval of time may exceed the duration of the experiment, as is clearly the case when no pain appears during the test, but develops a few minutes later when the patient has returned to his ward.²⁷

24. Homans, John: The Relation of Pain in Gastric and Duodenal Ulcer to Muscular Activity of the Stomach, *Am. J. M. Sc.* **157**:74 (Jan.) 1919. Reynolds and McClure.¹⁰ Palmer.¹³ Berg.¹⁸

25. MacLeod, Donald: Pain in Relation to Duodenal Ulcer, *Lancet* **2**:1358, 1929.

26. Hardy, T. L.: The Role of Hydrochloric Acid in the Causation of Gastric Pain, *Lancet* **1**:711 (April 6) 1929.

27. Palmer, W. L.: Certain Phases of the Ulcer Problem, *M. Clin. North America* **13**:413, 1929, cases I and II.

The same factors are operative when attempts are made to evoke pain by means of secretion induced by injection of histamine hydrochloride. Hardy's experiments gave negative results. We feel that the product of ulcer sensitivity and time were inadequate, for under proper conditions, ulcer pain may be initiated by histamine secretion as was evident in the earlier observations^{11b} and as we shall show again in the present report.

Hurst,^{28a} in 1929, discussed the subject of ulcer pain in considerable detail and concluded that while hydrochloric acid does constitute an adequate stimulus for the pain-producing mechanism, the effect is not due to mere contact of the ulcer with the acid. He was brought to this view by the known fact that the stomach and intestines are insensitive to tactile, thermal and chemical stimuli, and because he had satisfied himself, through the use of the stomach tube in the case of ulcers of the stomach and of the sigmoidoscope in those of the colon, that ulcers are as insensitive to these stimuli as is the healthy mucous membrane. The latent period noted in Palmer's earlier experiments was considered by him as additional evidence that the contact of the ulcer with the acid is not the cause of the pain. Hurst concluded that the "pain of duodenal ulcer depends upon an increase of tension which develops in some way when a small quantity of acid contents is present in the stomach." He elaborated on this view and developed the theory that this increase in tension occurs in the pyloric vestibule, and is due to achalasia and spasm of the pyloric sphincter plus deep peristaltic waves which by the time they reach the vestibule almost completely separate its contents from those of the proximal portion of the stomach. Consequently the pressure in the small distal segment rises unless the pyloric sphincter at the same time relaxes; if, for any reason, the sphincter does not relax, the pressure rises greatly.

The rise in pressure in the pyloric vestibule produces an abnormal degree of tension in the individual fibers of the muscular coat of this segment of the stomach. This is the actual cause of the pain, the rise in tension being the adequate stimulus required to produce the afferent nervous impulses which give rise to the sensation of pain.

The pain of gastric ulcer may occur independent of the condition of the pyloric sphincter, but Hurst ascribes this to an increase in pressure in the proximal portion of the stomach, the obstruction at the site of the ulcer being due apparently to a spasmodic hour glass constriction which "is frequently rendered more complete by the simultaneous pres-

28. (a) Hurst, A. F., and Stewart, M. J.: *Gastric and Duodenal Ulcer*, New York, Oxford University Press, 1929, pp. 26 and 154; (b) *ibid.*, p. 158; (c) *ibid.*, p. 44; (d) *ibid.*, p. 453.

ence of orthostatic hour glass constriction or organic hour glass constriction or by the presence of both."

The argument is based, in part, on the previously mentioned conclusion of Wilson²³ that ulcer pain disappears when the pylorus relaxes and the bulb fills out. Palmer's original roentgenologic observations on the complete absence of any relationship between pain and gastric peristalsis, spasm of the pylorus or spasm of the duodenal bulb, Hurst disregarded because they were made under artificial conditions, that is, with an acid solution of barium sulphate. He also pointed out that in three pairs of the roentgenograms shown, the lumen of the pyloric canal was half or less than half the width in those taken when pain was present compared with those taken after its disappearance, but he ignored the fact that direct fluoroscopic observation had shown this to be of no significance, owing to the constantly varying configuration of the stomach. Furthermore, it was obvious in these original roentgenograms, it seems to us, particularly in the first and last pair, that not only was the pylorus patent and the duodenal bulb well filled during the presence of pain, but also that a peristaltic wave of sufficient intensity to block off the contents of the pyloric vestibule from those of the main part of the stomach was not present. It is apparent, therefore, that the intragastric pressure in the vestibule must have been the same as that in the remainder of the stomach. Furthermore, it was clearly shown kymographically at that time that ulcer pain is entirely independent of changes in the intragastric pressure and therefore independent of changes in tension or tone in the body of the stomach or in the vestibule. In the work to be reported here we shall present further roentgenologic and kymographic confirmation of these findings.

In 1930, however, Smith, Paul and Fowler,²⁹ studying ulcer pain by the kymographic method, arrived at the conclusion that pain depends not on the reaction of the gastric content but on an increase in tone and peristaltic action. "In each case studied during distress, the pain corresponded with an increase in tone and the passage of a peristaltic wave." The intravenous injection of 1/50 grain (0.0013 Gm.) of atropine sulphate promptly relieved the distress. This work is described in greater detail in a subsequent article by Smith and Paul³⁰ in which they state that their "findings are in accord with the observations of Ginsburg, Tumpowsky and Hamburger, Carlson and Hardt . . . These observations support the contention of Hurst and Ryle, that the pain is primarily dependent on an increase in the intragastric tension." The

29. Smith, F. M.; Paul, W. D., and Fowler, W. M.: Alterations in the Gastric Function Associated with Gastric and Duodenal Ulcer, *Tr. A. Am. Physicians* **45**:377, 1930.

30. Smith, F. M., and Paul, W. D.: Studies on the Mechanism of the Pain of Peptic Ulcer, *Ann. Int. Med.* **5**:14, 1931.

method employed by Smith and Paul consisted of anchoring a water-filled balloon in the pyloric section of the stomach. The tracings shown do not entirely support the statement that "The pain corresponded with an increase in tone and the passage of a peristaltic wave." The method used by them does not record intragastric tension, but rather the pressure exerted by the antral musculature on an anchored bag. Their observations do, however, further confirm those of other workers, including Palmer, bearing on the adequacy of mechanical stimuli in the production of pain in sensitive ulcers.

Gutzeit,^{31a} in 1929, after considering the more or less contradictory evidence on the subject of gastric pain, concluded that its origin was not yet known. He considered that muscular contraction itself could be painful because von Bergmann had observed severe pain from the powerful contraction of the pyloric muscle around a piece of cabbage. Gutzeit himself during a gastroscopic examination had seen pain appear suddenly when the relaxed sphincter contracted and narrowed the gastric lumen, confirming an observation of Schindler's. This pain was exactly the same as the patient's spontaneous pain. It continued after the air distending the stomach had been allowed to escape through an opening in the gastroscope; hence it was not a pain from distention but one from muscular contraction. There is no reason to question these observations. It has been recognized for years that gastric motor activity may produce pain. The epigastric pangs of hunger have been shown by Cannon and Washburn,³² Carlson³³ and numerous other investigators to be due to contractions of the empty stomach. On the other hand, such peristalsis is commonly not accompanied by pain³⁴ and, as has been mentioned previously, painless spasm of the stomach has been observed. Furthermore, ulcer pain occurs during the digestive cycle, and digestive peristalsis is painless. The conditions under which gastric motor phenomena result in pain are not yet clear.

Gutzeit also pointed out that ulcer-like pains are not characteristic of ulcer alone but may be seen with pure gastritis without gross ulceration. These observations are in accord with the findings of Konjetzny,³⁵ but do not affect the problem of ulcer pain particularly. Gastritis is an

31. (a) Gutzeit, Kurt: *Die Gastroskopie im Rahmen der klinischen Magen-diagnostik*, Berlin, Julius Springer, 1929, p. 26; (b) *ibid.*, p. 77.

32. Cannon, W. B., and Washburn, A. L.: *An Explanation of Hunger*, Am. J. Physiol. **29**:441, 1912.

33. Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916.

34. Heinz, T. E., and Palmer, W. L.: *A Study of the Effect of Insulin on Gastric Motility*, Proc. Soc. Exper. Biol. & Med. **27**:1047, 1930.

35. Konjetzny, G. E.: *Entzündliche Genese des Magen-Duodenalgeschwürs*, Arch. f. Verdauungskr. **36**:214, 1925.

ulcerative process. The lesions are small and superficial, but nevertheless ulcerative and surrounded by an inflammatory reaction. Furthermore, Gutzeit observed, and we likewise have repeatedly noted, that there is no correlation between the size of the lesion and the severity of the pain. Gutzeit ascribes this variability to individual differences in response to pain, but does not know whether this is due to variations in conduction or perception of pain or to other factors.

Christensen,³⁶ working in Knud Faber's clinic in Copenhagen, made a careful study of so-called "hunger pain" in 1931. By "hunger pains" she meant the "cardialgia appearing at times when the stomach is presumably empty or nearly empty, and of which the patient gives the information either that it is relieved by the intake of food or, at any rate, that he has never tried if it is so." She gathered her material without attaching any particular importance to the verification of the diagnosis of ulcer and insisted merely on the presumably unquestionable presence of the so-called "hunger pain." However, in the protocols it is apparent that the diagnosis of ulcer was made in the majority of the cases. It seems fair to assume that most of the pain which she studied was ulcer pain. She concluded:

. . . the pains have never been present without the gastrographic curve showing a concurrent contraction period. There was never any registration of an attack of pain during a period of absolute rest. The pain registration would always begin sooner or later after a contraction period had started and they would cease when this period was replaced by absolute rest or a few minutes after.^{36b}

The pain registered by the patients was of two types: first, a continuous pain throughout the period of contraction, and second, intermittent pain. Examination of the gastric content was interpreted to show that

. . . there was no relation whatever between the spontaneous variations in the acidity of the stomach content and the appearance or the intensity of the pain. Nor was the pain affected by the artificial production of very low acidity values (acid deficit of several hundreds).^{36c}

Relief of pain following the ingestion of sodium bicarbonate without any influence on the gastric contractions was noted by her as it had been noted by Ortmayer.³⁷ Christensen thought it

. . . reasonable to assume that the relief has nothing to do with the alkaline reaction and that it is due to the carbon dioxide which is liberated on the mixture of hydrochloric acid and sodium bicarbonate. For, as is well known, carbon dioxide has a strong anesthetizing effect on the mucous membrane. . . . These examinations then show no relation whatever between the variations in the acidity of

36. (a) Christensen, Olive: *Pathophysiology of Hunger Pains*, Copenhagen, 1931, p. 78; (b) *ibid.*, p. 79; (c) *ibid.*, p. 102; (d) *ibid.*, p. 103.

37. Ortmayer, Marie: *Gastric Motor Activity in Patients with Peptic Ulcer*, *Arch. Int. Med.* **35**:423 (April) 1925.

the stomach content and the variations in the spontaneous pain that may be observed during a single examination of a few hours' duration. This, however, does not exclude the possibility that the pain may be appearing only on days or in periods when the acidity on the whole is rather high.^{36d}

Her criticism of Palmer's earlier work is based apparently on two points: first, that the pain usually studied was an "artifact pain" produced by repeatedly filling the inflamed stomach with large amounts of an acid sufficiently concentrated to produce an uncomfortable burning when injected into a normal stomach, and second, that she could see no correlation between the acidity of the gastric content at a given time and pain at the same or nearly the same time. In answer to the first criticism, that the pain produced was "artifact pain," it is necessary only to point out that Christensen seems to have overlooked the fact that pain was produced repeatedly by the introduction of *normal gastric content* and of perfectly *physiologic concentrations of hydrochloric acid* (from 0.2 to 0.3 per cent). The second criticism, the lack of correlation between the intensity of the pain and the degree of acidity present, is also not valid, for it ignores the factor of *time*, the significance of which has become increasingly apparent to us throughout our work. In some very sensitive ulcers severe pain may be produced immediately by the introduction of acid into the stomach; in others, a very variable interval elapses before distress appears. The pain may begin as a mild discomfort, gradually and continuously increasing in severity until it becomes an excruciating cramp. This gradual increase in the severity of the pain, it seems to us, must also be the result of time. As was mentioned previously in discussing Hardy's work, one must consider pain as the product of ulcer sensitivity, acid concentration and time.

In 1927 one of us (W. L. P.) examined some of Christensen's tracings. They are excellently reproduced in her monograph. There can be no question as to the facts presented by her, but there is a definite difference in opinion as to the interpretation of these facts. The intermittent pain described by Christensen in ulcer is similar in all respects to the intermittent pain described by Carlson¹⁵ and by us. This distress is definitely correlated with gastric activity. The continuous spontaneous pain seen by Christensen is correlated with gastric activity only to the extent that it appears at some time after the beginning of a period of contraction and continues until after the end of this phase. It was not found to appear during a period of rest. Christensen worked with patients whose stomachs contained only a small amount of content. The experimental subject was allowed to lie on his back, propped up slightly by pillows. Under these conditions it is certain that the stomach does not empty its content continuously into the duodenum, for it may be shown roentgenologically that in the supine position, small amounts

of barium sulphate will remain in the most dependent portion of the stomach, the fundic region, during periods of gastric quiescence until, with the onset of peristalsis, the barium sulphate is gradually carried up over the spine into the pyloric segment and the duodenum, bathing the surface of the ulcer with chyme. With a sufficiently sensitive mechanism, an adequate concentration of hydrochloric acid and time, pain results. It is noteworthy that free hydrochloric acid was present in Christensen's experiments at the time of pain. The continuous pain observed by her in periods of gastric activity is thus explained. Careful examination of the numerous protocols has failed to reveal to us any evidence opposed to this concept.

A significant study of the effect of nitrites on pain and on the motility of the gastro-intestinal tract has recently been reported by Beams.³⁸ He confirmed the earlier work of Holmes and Dresser³⁹ and found that in 95 per cent of the cases studied, nitrites inhibited gastric peristalsis and diminished gastric tone. The effect lasted from two to five minutes with amyl nitrite, and from five to ten minutes with spirits of glyceryl trinitrate.

Amyl nitrite gave complete relief from pain in twelve of the twenty patients with duodenal ulcer, partial relief in four, and no relief in four. The pain was relieved for from five to twenty minutes. . . . Six (of the ten) patients with gastric ulcer obtained relief of pain for from five to fifteen minutes after inhalation of amyl nitrite, whereas in four patients with penetrating gastric ulcer the pain was not controlled. In three patients with pyloric stenosis proved by operation in whom visible peristalsis was observed, amyl nitrite not only relieved the pain but caused cessation of the peristalsis. The peristalsis disappeared more promptly than the pain, but reappeared in from three to five minutes while the pain was relieved for from five to ten minutes.

Apparently in those cases in which temporary relief of pain occurred, it was due to the effect of the medication on the musculature, although the other effects of the medication, such as throbbing in the head, slight dizziness or a warm flushed feeling, may have played more of a rôle than has been recognized. Beams feels that this evidence supports the theory that ulcer pain is dependent on the motility and tone of the stomach rather than directly on the acidity, although he considers the acidity to be an important factor in the pain. It is to be noted, however, that he did not observe ulcer pain in the continued absence of free acidity. The further significance of his observations will be discussed later.

38. Beams, A. J.: The Effect of Nitrites on the Motility of the Gastro-Intestinal Tract: Clinical Study, *Arch. Int. Med.* **49**:270 (Feb.) 1932.

39. Holmes, G. W., and Dresser, Richard: The Use of Amyl Nitrite as an Anti-Spasmotic, *Am. J. Roentgenol.* **19**:43 (Jan.) 1928.

Vanzant and Snell⁴⁰ have recently reported a study of the effect of the injection of nonspecific protein on the pain of ulcer and on gastric secretion with the following conclusions:

In cases of ulcer, the injection of foreign protein was frequently followed by a gratifying reduction in the amount of pain and distress. This clinical improvement was not associated with any consistent lowering of the gastric acidity and there was no correlation between the degree of acidity found at any one time and the amount of pain complained of. . . . There was some evidence to indicate that more lasting relief of symptoms can be expected in those cases in which the secretion is reduced after treatment. . . . We have no exact information which would warrant our making guesses as to the mechanism which in some cases produces prompt relief of pain and discomfort.

It has been recognized for many years that during the pain-free periods of ulcer the gastric acidity is practically the same as during the periods of pain. This has little bearing on the rôle of acidity in the production of pain, for in the one instance the acid acts on a sensitive, and in the other instance on an insensitive, mechanism. Of the three variables, sensitivity of the ulcer, time and concentration of the acid, Vanzant and Snell studied chiefly the acid factor. They apparently found it to be invariably present, but were unable to correlate the degree of acidity with the severity of the pain at a given time. This was probably due to the fact that the difficult variables of time and of sensitivity of the ulcer entered in.

Meyer, Fetter and Strauss⁴¹ concluded from their investigations on the relation of ulcer pain to gastric motility and acidity that "the patients were found to fall into two classes: (1) those who had pain response to an acid stimulus but showed no pain in relation to gastric motility and (2) those who had no pain response to an acid stimulus but had pain during periods of gastric motility." In their case 1, illustrative of eight showing pain in response to an acid stimulus, distress developed with the perfectly physiologic concentrations of acid found in the patient's own gastric juice—a significant observation confirming our own work—and appeared also following the introduction of acid into the stomach; relief was obtained on withdrawal of the acid and the administration of sodium bicarbonate. Gastric motility, as recorded kymographically, was independent of pain. In case 2, illustrative of six cases showing pain during periods of gastric motility, pain did not develop from the injection of acid, although this was tried on two occasions. Three days later a relationship of the pain to gastric motility was demon-

40. Vanzant, F. R., and Snell, A. M.: The Effect of Injection of Nonspecific Protein on the Pain of Ulcer and on Gastric Secretion: A Clinical and Experimental Study, *J. Clin. Investigation* **11**:647 (July) 1932.

41. Meyer, Jacob; Fetter, Dorothy, and Strauss, A. A.: The Relation of Pain in Peptic Ulcer to Gastric Motility and Acidity, *Arch. Int. Med.* **50**:338 (Aug.) 1932.

strated. The failure of the "acid test" to evoke pain in this instance is somewhat puzzling, but the phenomenon is one observed by us also, and discussed elsewhere.⁴² However, we feel that Meyer, Fetter and Strauss are not justified in excluding the acid factor. The patient's stomach was known to secrete free hydrochloric acid, a free acidity of 25 having been found on one occasion and one of 35 on another. No determination of the degree of gastric acidity was made during the motility test in this experiment. In view of the aforementioned observations¹³ with regard to acid sensitization as a prerequisite in the pain of ulcer it seems necessary to insist that to consider motility as the sole cause of the pain it must be shown to be effective in the *continued absence of free hydrochloric acid*. This evidence has not been adduced as yet.

Various observers have attempted to induce ulcer distress by the direct application of acid to the surface of the ulcer by means of a duodenal tube or at operation. Reynolds and McClure,¹⁰ using a Rehfuß tube, the tip of which was ascertained by fluoroscopy to be in the duodenal bulb at the site of the lesion, were unable to produce pain or any other subjective sensation even though pylorospasm, cessation of gastric peristalsis and duodenal antiperistalsis were induced. Schüle,⁴³ on the other hand, using the same technic, was successful and suggested it as a method for determining the presence of a duodenal ulcer. Meyer, Fetter and Strauss⁴¹ introduced 50 cc. of a 0.5 per cent solution of hydrochloric acid directly into the duodenum and apparently produced pain in some cases (number not stated). These same observers failed to produce distress in four cases of gastric or duodenal ulcer in which hydrochloric acid in dilutions of 0.5 per cent, 1 per cent and 5 per cent was applied directly to the ulcer during operation under local anesthesia. Two of these patients previously had given definitely positive responses to the "acid test" and two to the "motility test." Failures such as these in the production of pain by the application of acid at operation are not surprising, for while the factors of ulcer sensitivity and of acidity may be adequate under ordinary conditions for the production of pain, the time factor is almost necessarily inadequate. The surgeon who applies the acid to the surface of the ulcer is naturally unwilling to wait more than a few minutes to observe its effect. Hence in order for such an experiment to be positive it is necessary for the ulcer to be at the moment in such a high state of irritability that the application of acid will evoke pain instantly or within a few moments. This is rarely the case, as is shown by the interval of from several minutes to an hour or more which usually elapses even under normal conditions between the development of a good acidity (be it from the

42. Palmer (footnotes 11 and 12).

43. Schüle, A.: Zur klinischen Diagnostik des Ulcus duodeni, München. med. Wchnschr. **73**:1191, 1926.

introduction of acid, the secretion induced by injection of histamine hydrochloride, or the secretory response to ingestion of food) and the appearance of pain. Consequently we are not inclined to attach much significance to these seemingly crucial but negative experiments.

Meyer, Fetter and Strauss did not mention whether or not pain was produced by mechanical stimulation of the ulcer area, as by pinching, although they stated that traction on the mesentery was painful.

Westphal and Katsch,⁴⁴ in operating on a patient with duodenal ulcer under local anesthesia, observed a powerful contraction of the pylorus associated with severe typical hunger pain as the result of electrical stimulation of the gastric antrum. They considered the normal mechanism of pain to be that of pylorospasm induced by an exaggerated acid reflex. Lennander,⁴⁵ in operating on a perforated gastric ulcer under local anesthesia, noted that the inflamed walls of the stomach and intestine were quite insensitive to mechanical stimuli. This observation was confirmed by Morley⁴⁶ in two cases. Kinsella,⁴⁷ on the other hand, found experimentally that the normally insensitive bowel could be rendered sensitive to mechanical stimuli by the rapid injection of saline solution into the wall of the bowel. Ivy⁴⁸ had a similar experience.

Dragstedt and Palmer⁴⁹ reported one positive experiment in the mechanical and chemical production of ulcer pain during an operation on a patient under local anesthesia. The duodenal ulcer in this case was highly irritable as was shown by the excruciating spontaneous pain and the very severe pain produced by the acid test on the morning of operation. Dr. Dragstedt's description of his observation is as follows:

A puckered scar was visible on the anterior wall of the duodenum about one centimeter distal to the pylorus. On very gently rubbing the serosa of this scar with the gloved finger the patient complained of pain similar to his ulcer distress. This pain persisted after the rubbing was discontinued. The patient was then told that something would be done to relieve his distress entirely, whereupon the region of the ulcer was rather firmly compressed between the thumb and forefinger of

44. Westphal, Karl, and Katsch, Gerhardt: *Das neurotische Ulcus duodeni*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:402, 1913.

45. Lennander, K. G.: *Beobachtungen über die Sensibilität in der Bauchhöhle*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **10**:94, 1902.

46. Morley, John: *Abdominal Pain*, New York, William Wood & Company, 1931, p. 71.

47. Kinsella, V. J.: *The Mechanism of Pain Production in Abdominal Visceral Disease with Special Reference to the Pains of Peptic Ulcer*, M. J. Australia **1**:64 (Jan. 21) 1928; *Some Problems of the Normal and Pathological Physiology of the Stomach*, Lancet **1**:1130, 1929.

48. Ivy, cited by Alvarez, W. C.: *The Mechanics of the Digestive Tract*, New York, Paul B. Hoeber, Inc., 1928, p. 145.

49. Dragstedt, L. R., and Palmer, W. L.: *Direct Observations on the Mechanism of Pain in Duodenal Ulcer*, Proc. Soc. Exper. Biol. & Med. **29**:753, 1932.

the operator and massaged gently but firmly. This produced severe distress. Several guide threads of fine silk were now introduced into the anterior wall of the pyloric antrum and by means of these traction was made on the duodenum pulling it toward the left. Every time this traction was made the patient complained of severe pain resembling his ulcer distress. While this distress was present and while the traction was continued twenty cubic centimeters of five per cent sodium bicarbonate solution were injected by means of a hypodermic needle into the lumen of the pylorus. The distress was almost immediately relieved, and this relief persisted for about five minutes. Twenty cubic centimeters of 0.5 per cent hydrochloric acid were then injected into the first portion of the duodenum in the same way, and almost immediately the patient complained of a burning type of pain. This persisted until an injection of sodium bicarbonate solution was made. The relief obtained from this last injection was not as striking as at first, and it did not persist. After about three minutes the patient complained of severe cramping pain which radiated up into his chest. This radiation had been frequently noted before in association with a cramping type of pain. Simultaneous with the appearance of this cramping pain there appeared a deep circular contraction ring just distal to the ulcer. This local spasm of the duodenum after a while passed distally only to be succeeded by several subsequent similar spasms. All during this time the patient complained of very severe cramp-like pain. It is interesting in view of this observation that several peristaltic waves were seen passing over the pyloric antrum at a time when no distress was experienced.

In our judgment these observations are highly significant. They show clearly that the ulcer pain in this case arose in the lesion itself, or in its immediate neighborhood, and not in the pylorus or in the gastric antrum. Furthermore, it was produced *mechanically* by rubbing or pinching the serosa above the lesion or as the result of a circular contraction ring appearing just distally to the lesion, and *chemically* by the injection of acid into the lumen of the duodenum where it presumably came into contact with the surface of the ulcer. Similarly the injection of alkali relieved the pain.

METHODS

The methods employed in the work to be herewith reported have been similar to those previously used and have included: clinical observation of the acidity of the gastric content during spontaneous distress, the production of ulcer pain by physiologic solutions of hydrochloric acid and by stimulation of gastric secretion with histamine hydrochloride, kymographic and roentgenologic studies of the stomach during distress, and observations on the effect of atropine sulphate and of calcium chloride on ulcer pain. We have not attempted to tabulate our data, feeling that the results are best presented by a careful consideration of certain illustrative protocols, kymographic tracings and roentgenograms. The group that was studied includes patients with benign gastric ulcer, duodenal ulcer and gastric carcinoma, in all of whom the clinical diagnosis was confirmed roentgenologically, except for one patient with recurrent ulceration following partial gastric resection in whom the diagnosis was based on clinical evidence only. Several of the patients were also operated on and the diagnosis was thus confirmed.

RESULTS

The following protocol was obtained during a study of the patient with recurrent ulceration following partial gastrectomy. The initial lesion in this case had been a duodenal ulcer for which a gastroenterostomy had been performed. A gastrojejunal ulcer had then developed, as was demonstrated at the second operation. A partial gastrectomy was performed. Following this the patient's typical ulcer distress recurred, accompanied at least on one occasion by tarry stools. This case is included because it is the only one of its kind which we have been able to study, and because the results are so typically those of ulcer distress.

CASE 1.—7:45 a. m.: The patient was awakened with pain which was relieved by a hot bath at 8.

8:15: Four ounces each of cream and milk were given.

9:50: The typical distress appeared below or around the navel on the left side.

10:20: The pain continued, with nearly the usual severity. Aspiration of the stomach (Rehfuss tube) yielded 17 cc. of green fluid, with a free acidity of 19. The distress became less.

10:25: The stomach was aspirated: 55 cc. of thick yellow green bile was obtained; the free acidity was 0. The distress was nearly gone.

10:30: The distress was entirely gone.

11:02 to 11:05: Two hundred cubic centimeters of a 0.4 per cent solution of hydrochloric acid was injected. Distress appeared during the injection, at 11:03.

11:10: The pain was quite severe, worse than at any time that day.

11:17: The patient felt very uncomfortable, as evidenced by writhing and moaning. Nausea appeared.

11:20 to 11:25: The stomach was aspirated, yielding 250 cc. of yellow liquid with a free acidity of 37. The distress at once became less severe and gradually diminished.

11:45: Aspiration of the stomach yielded 15 cc. of yellow liquid; the free acidity was 10.

11:50: The distress was practically gone; only a slight soreness remained.

11:55: The pain returned.

12:00 The stomach was emptied; 10 cc. of cloudy blood-tinged juice was obtained; the free acidity was 33.

12:10 p. m.: The pain continued; aspiration of the stomach yielded 6 cc. of fluid with a free acidity of 30.

12:20: The pain still continued, but was mild; aspiration of the stomach yielded, first, 12 cc. of clear fluid, and then 8 cc. of thick yellow fluid. The free acidity of the mixture was 18.

12:30: The distress was nearly gone. The stomach yielded 7 cc. of clear juice with a free acidity of 16.

12:40: The distress was practically gone. Aspiration yielded 20 cc. of cloudy thick yellow liquid with a free acidity of 0.

12:48 to 12:50: One hundred cubic centimeters of a fortieth-normal solution of sodium hydroxide was injected.

1:10: The patient was more free from distress during the last twenty minutes than he had been all forenoon. He felt entirely comfortable. The stomach was emptied, and 30 cc. of cloudy liquid was obtained; the free acidity was 6.

1:15: The patient became more uncomfortable.

1:25: The pain gradually grew more severe and was now as bad as ever. The stomach was aspirated, yielding 27 cc. of cloudy gray juice with a free acidity of 44. The patient groaned and writhed with pain.

1:35: The pain continued to be severe. The stomach was emptied; 20 cc. of cloudy gray liquid with a free acidity of 43 was obtained. There was slight easing of pain.

1:37 to 1:40: One hundred cubic centimeters of a tenth-normal solution of sodium hydroxide was injected.

2:07: The pain was nearly gone; the patient stated that he felt much better than previously.

2:10: The stomach was emptied, yielding 60 cc. of a yellow liquid with free acidity of 0. The pain was practically gone.

In this experiment spontaneous pain was present, with a free acidity of 19. Following aspiration, bile-colored duodenal content appeared in the stomach in sufficient quantity to neutralize the free acid completely. This was accompanied by complete relief of the distress for thirty minutes. Very severe distress was then produced immediately by the injection of 200 cc. of a solution of approximately 0.4 per cent hydrochloric acid. The stomach was aspirated from 11:20 to 11:25 a. m. with gradual but almost complete relief by 11:50. Ten minutes later the distress had returned. The free acidity was found to have risen to 33. The pain continued; the free acidity was still 30. Ten minutes later the free acidity had dropped; more duodenal content had appeared, and twenty minutes later, with a free acidity of 0, the pain was gone. Following the administration of 100 cc. of a fortieth-normal solution of sodium hydroxide the pain did not reappear for twenty-five minutes. It then gradually increased, and ten minutes later became very severe, at which time the free acidity was found to be 44. The pain continued, and the free acidity remained high until 1:40 p. m., when 100 cc. of a tenth-normal solution of sodium hydroxide was given, followed by relief in twenty minutes. Considering the constantly changing conditions produced by the irregular discharge of duodenal content into the stomach and the very important factor of *time*, it seems to us that this experiment demonstrates clearly the relationship between gastric acidity and ulcer pain.

Figure 1 shows the kymographic tracing made with the usual technic (a water manometer, a balloon located in the stomach and containing approximately 120 cc. of air, an air-filled system) in the case of a patient with an active, highly sensitive duodenal ulcer. Spontaneous pain was present at the beginning of the experiment (*A*, 11:55 a. m.), with a gastric acidity of 60, total 90. The stomach was emptied, 40 cc. being obtained, and the pain gradually subsided at *B* and *C* (12:03 and 12:06 p. m.), suddenly recurring four minutes later, at *D*. The sudden exacerbation

It is highly significant, however, that at *E* (12:13) the free acidity was still 57. The stomach was continuously aspirated, and at *H* (12:20) the pain was entirely gone, although some soreness persisted. Continuous aspiration of the stomach for twenty-five minutes from *H* to *I* (gastric content, 40 cc.; free acidity, 60; total, 85) was not accompanied by pain. However, when 30 cc. of the aspirate obtained at *A* was reintroduced into the stomach two minutes later at *J*, severe pain appeared in six minutes (*K*), quickly becoming intolerable (*L*). Its intensity may be inferred from the marked increase in the amplitude of the respiratory excursion. This is a phenomenon which we have noted in this patient only. The stomach was immediately emptied (*M*) of 30 cc. of gastric juice (free acidity, 62); four minutes later (*N*) the pain was approximately 50 per cent better; six minutes later (*O*) 4 Gm. of calcium carbonate was given in 20 cc. of water. The pain disappeared completely within six minutes (*Q*) after the injection of the alkali. The experiment shows clearly the relief from ulcer distress by continuous aspiration of the stomach, and the production of excruciating pain by the introduction of the physiologic irritant, the patient's own gastric juice containing a rather high free acidity. This distress was relieved by emptying the stomach and injecting alkali. It was not accompanied by any significant change in gastric motility or intragastric pressure.

The following protocol, obtained in the study of a case of duodenal ulcer, shows that the pain-producing mechanism of ulcer is not desensitized by the injection of atropine sulphate.

CASE 2.—2:45 p. m.: One milligram of atropine sulphate was injected intravenously. No pain was present.

2:50: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was injected.

2:52: The pain came on suddenly.

2:55: Severe pain was present. The patient cried, doubled over with pain and rocked back and forth in her chair. The pulse rate was 122.

3:00: The patient complained of faintness; the pain continued to be severe, and the patient had to be supported in a chair. The stomach was aspirated and washed with 200 cc. of water.

3:05: The pain was somewhat relieved; washing of the stomach was continued with 200 cc. of water.

3:10: The pain was only slight; the washing with 200 cc. of water was continued.

3:15: The pain ceased; the washings showed no free acid.

The severity of the pain is noteworthy. Smith, Paul and Fowler²⁰ have shown that spontaneous ulcer distress may be relieved rather promptly by the intravenous injection of atropine sulphate. The mechanism of this relief will be discussed later. In this experiment, however, the production of excruciating pain by means of the acid test immediately

after the administration of atropine sulphate intravenously certainly shows that the relief described is not due to desensitization of the pain-producing mechanism.

The following protocol from another case of duodenal ulcer illustrates the same point. A kymographic record was made but is not reproduced here.

CASE 3.—2:45-4:00 p. m.: There was a normal gastric hunger period without pain.

4:23: The stomach was emptied; 20 cc. of gastric juice was obtained; the free acidity was 68; total, 77.

4:25-4:38: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was administered by tube.

4:42: Pain in the back appeared.

4:46: Typical epigastric pain appeared.

4:51: One milligram of atropine sulphate was injected intravenously.

5:10: The steady continuous pain became more severe.

5:20-5:24: The pain remained the same. Two hundred cubic centimeters of tenth-normal solution of sodium hydroxide was given by tube.

5:28: There was intense nausea with emesis of about 100 cc. of clear liquid; this was lost. The pain was completely relieved.

In this experiment the atropine sulphate was given during the period of pain with no relief whatsoever. On the other hand, relief came quite promptly after the introduction of alkali.

The kymographic tracing shown in figure 2 illustrates the failure of atropine sulphate to give relief and the direct relationship between pain and free acidity. The spontaneous distress present at the beginning of the tracing (*A*, 11:15 a. m.) disappeared at *B* (11:20) after the stomach had been aspirated at *A*, yielding a free acidity of 45. The distress recurred at *C* (11:30), and 20 cc. of gastric content, free acidity, 60, was obtained. At *D* the pain was about half gone, and at *E* (11:43) it had completely disappeared. Continuous aspiration of 45 cc. of gastric juice, free acidity, 64, from *E* to *F* (11:43 a. m. to 12:30 p. m.) kept the patient free from distress for forty-seven minutes. One milligram of atropine sulphate was given intravenously at *G* (12:32), and at the same time 35 cc. of the gastric juice with a free acidity of 64 aspirated at *F* was reintroduced. Severe pain appeared in three minutes (*H*), becoming intense three minutes later, as the increase in the amplitude of the respiratory excursion shows. It is noteworthy that here again the stimulus employed was the perfectly physiologic one of the patient's own gastric juice. The distress subsided spontaneously twelve minutes later at *K* (12:50). At *L* only 10 cc. of gastric juice, free acidity 60, was found in the stomach. Sixty cubic centimeters of a 0.5 per cent solution of hydrochloric acid was then introduced, agonizing pain resulting in three minutes. The pain was unbearable at *N*. The

CASE 4.—2:47 p. m.: The stomach was emptied, and yielded 30 cc. of clear liquid with a free acidity of 59; total, 88.

2:53: One milligram of atropine sulphate was injected intravenously.

3:21: Two hundred cubic centimeters of 0.5 per cent solution of hydrochloric acid was given by tube. The pain which appeared during the injection was quite severe and typical.

3:35: One gram of calcium chloride was injected intravenously.

3:44: The pain was still present but much less severe.

3:50: There was some nausea; the pain was still present.

3:53: The pain was nearly gone; the nausea persisted.

4:03 to 4:06: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was given by tube.

4:10: The nausea persisted.

4:20: The nausea decreased.

4:30: The nausea was gone.

4:45: Twenty cubic centimeters of gastric content was aspirated; the free acidity was 78; total, 82.

5:10: Two hundred cubic centimeters of a 0.5 per cent solution of hydrochloric acid was given.

6:12: The stomach was aspirated and yielded 190 cc. of a clear liquid; the free acidity was 91; total, 96. There was no pain.

Here again atropine sulphate failed to desensitize the pain-producing mechanism, but the severe pain produced by the injection of acid decreased quite rapidly and promptly after the administration of calcium chloride. It is important to note that this relief was accompanied by nausea, and that nausea persisted after the pain had been relieved. The injection of 200 cc. of a 0.5 per cent solution of hydrochloric acid did not produce pain, and the nausea continued. The third injection of acid also failed to produce pain. The probable mechanism involved in this phenomenon will be discussed later.

Figure 3 shows the kymographic study of a similar experiment. At *A* (3:05 p. m.) the stomach was aspirated, yielding 20 cc. of gastric juice, free acidity, 42. Moderate pain appeared at *B* (3:45) and became excruciating at *C*, *D* and *E*. The stomach was aspirated between *E* and *G*, yielding a free acidity of 64. The intravenous administration of 10 cc. of a 10 per cent solution of calcium chloride ending at *G* gave prompt but very brief relief. At *J* (4:02) 95 cc. of a 0.3 per cent solution of hydrochloric acid was injected. The free acidity was 65. At *L* (4:07) the patient was again doubled up with pain which continued, quickly becoming intolerable (*M*) until the stomach was aspirated (*N*), yielding 95 cc. of contents, free acidity, 64. At *O* the pain was half gone. From *P* to *S* continuous aspiration yielded 40 cc. of gastric content, free acidity, 45. At *T* 90 cc. of the gastric juice aspirated at *N*, free acidity, 64, was reinjected. Pain reappeared at *U*, rapidly becoming severe; it was momentarily decreased by the injection of 1 mg. of atropine sul-

phate intravenously at *V* (4:39), but quickly became excruciating again at *X* (4:43), the patient writhing in pain from *X* to *Y*. At *Y* (4:45) the stomach was aspirated, 70 cc. of gastric content with a free acidity of 60 being obtained. Two grams of sodium bicarbonate in 30 cc. of water was given at *Z*, with complete relief eleven minutes later, at *Z*₁. Here one notes that both calcium chloride and atropine sulphate

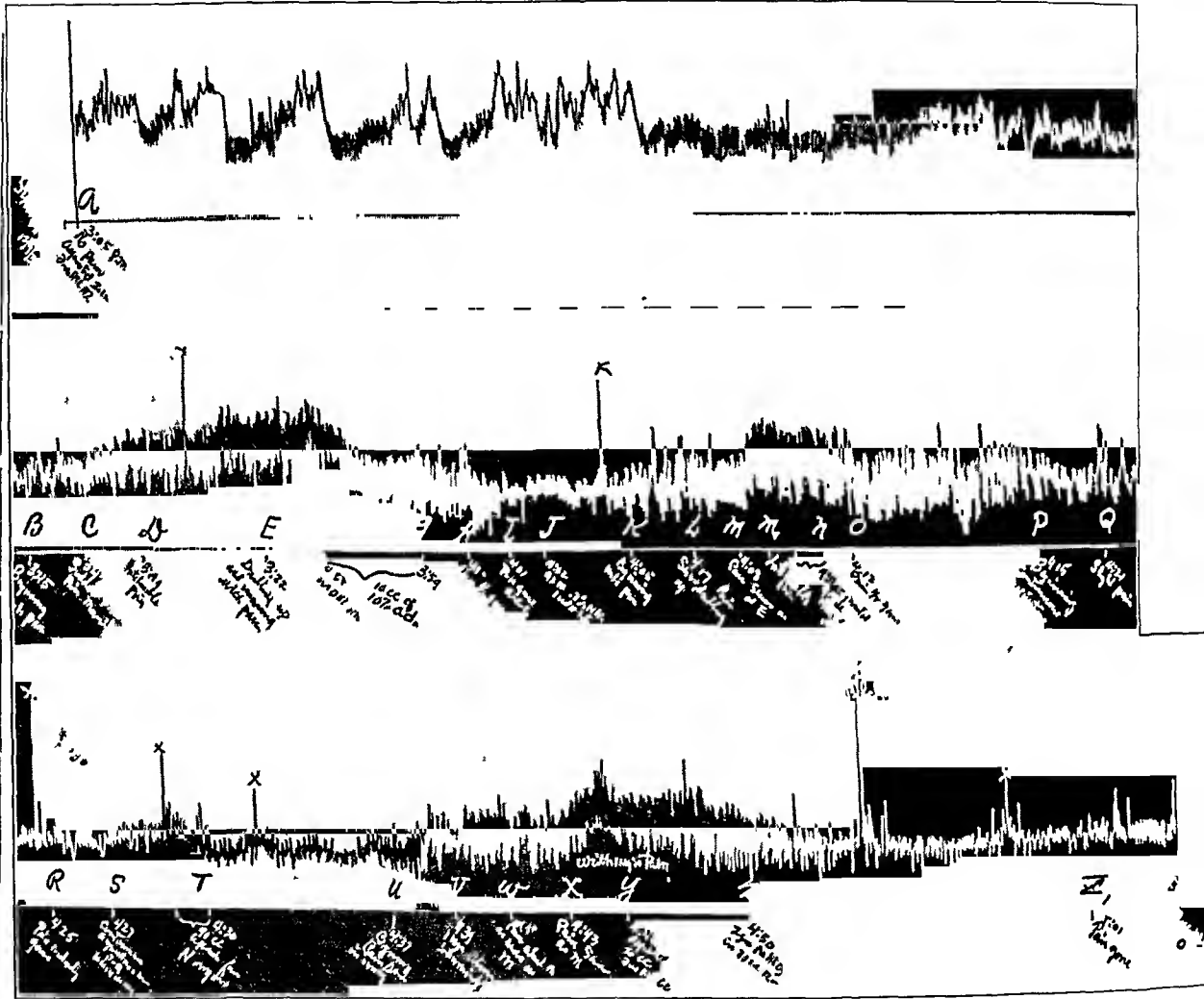


Fig. 3.—Kymographic tracing from a case of active gastric ulcer showing: (1) transitory relief from ulcer pain by the intravenous injection of calcium chloride; (2) the failure of atropine sulphate to relieve distress induced by the reinjection of the patient's own gastric juice, and (3) relief from emptying the stomach and administering sodium bicarbonate.

failed to desensitize the pain-producing mechanism, and again that excruciating pain was produced by the reintroduction of the normal physiologic irritant, the patient's own gastric juice. At *XX* samples of gastric content contained no acidity.

Similar studies have been made in a case of carcinomatous gastric ulcer with a high free acidity, as in the following protocol:

CASE 5.—2:07 p. m.: There was a constant dull pain.

2:20: Ten cubic centimeters of the gastric content was aspirated; the free hydrochloric acid was 38; total, 83.

2:35: The pain grew more severe.

3:00: The pain continued unchanged. One gram of calcium chloride was given intravenously.

3:04-3:08: The pain was nearly gone.

3:17: A mild dull pain continued.

3:18: One milligram of histamine hydrochloride was given subcutaneously. The stomach was aspirated, yielding 10 cc. of gastric content with a free acidity of 40; total, 75.

3:30: The pain became severe; headache developed.

3:35: The pain increased; there was emesis of 90 cc. of liquid with thick mucus. The free acidity was 37; total, 55.

3:43: The patient writhed and rolled in great agony.

3:44: Four grams each of sodium bicarbonate and calcium carbonate were given by mouth.

3:48: The pain decreased; the patient stated: "The worst of it is gone."

3:54: The pain was slighter than at any time in the afternoon.

The distress in this instance disappeared for a brief time after the administration of calcium chloride and then recurred. One milligram of histamine hydrochloride was given subcutaneously; this was followed by an increase in the pain, so that twenty-five minutes later the patient was writhing and rolling about in agony. Four grams each of calcium carbonate and sodium bicarbonate were given by mouth with almost complete relief in ten minutes.

Figure 4 is a kymographic tracing of the same patient. At *A* (2:18 p. m.) type I hunger contractions were present. At *B* the stomach was emptied of 20 cc. of the gastric content, free acidity 72, total 92. Typical pain appeared at *C* (2:58) and increased until at *F* (3:08) the patient writhed in agony. From 3:09 to 3:12, 10 cc. of a 10 per cent solution of calcium chloride was given intravenously. At *G* the pain seemed to be 75 per cent relieved, but it quickly increased again at *H* (3:18), and at *I* the patient was again writhing. (The irregular fluctuations in the curve are due to changes in position, etc.) At *J* 1 mg. of atropine sulphate was given intravenously, but agonizing pain continued at *K*, the patient exclaiming, "God, it does hurt me!" The pain continued at *L*. At *M* the stomach was emptied, 140 cc. of clear gastric juice with a free acidity of 45 being obtained. This was followed in eight minutes by 75 per cent relief of the pain present at *N*. It increased slightly at *O* but at *Q* was completely gone. One hundred and thirty cubic centimeters of the gastric content with a free

time only 5 cc. of content, free acidity of 45, total 66, was found in the stomach. The free acidity present was adequate for the production of pain, as has just been shown (*R* to *U*). The explanation for the relief from pain in spite of the high free acidity is probably to be found in the very small amount (5 cc.) of gastric content present. It may be shown roentgenologically that in the empty stomach, collapsed by its own musculature and by intra-abdominal pressure, the very few cubic centimeters of gastric content present is located in the fundic portion just below the air bubble. Large quantities of gastric content are required if the surface of the lesion is to be bathed by acid chyme, and pain produced. One-half milligram of histamine was then given sub-

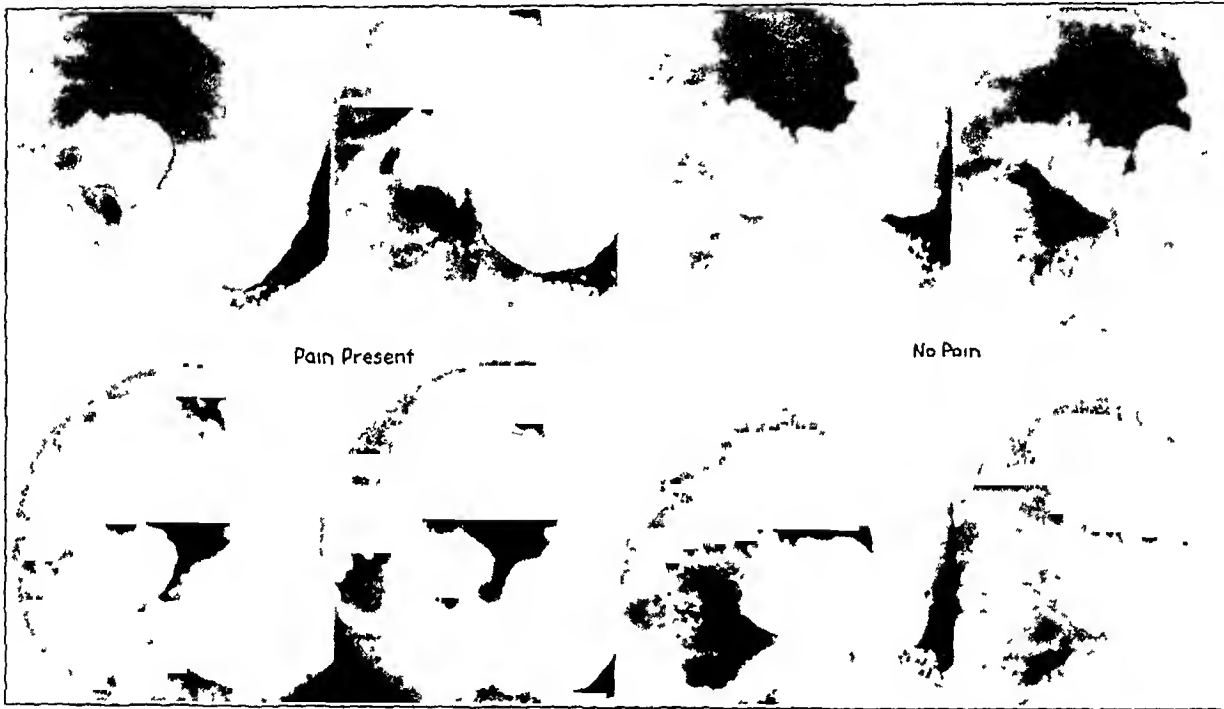


Fig. 5.—Roentgenograms made in a case of benign gastric ulcer.

cutaneously at *W*; headache and flushing of the face appeared almost at once. Pain appeared twenty-seven minutes later at *Y*, becoming quite severe at *A*₁ and agonizing at *B*₁, when the patient exclaimed "It hurts to beat hell!" At *C*₁ the pain was so excruciating that the patient, in clinching and grinding his teeth, shut off the tube connected with the manometer and interfered with the recording of intragastric pressure. Two grams each of calcium carbonate and sodium bicarbonate were given at *D*₁ with a gradual decrease in pain from *D*₁ to *E*₁, at which time it disappeared entirely.

In this observation of the behavior of the excruciating pain seen in a patient with a carcinomatous ulcer associated with a high gastric acidity, it may be seen that the pain was only temporarily allayed by the intravenous injection of calcium chloride, that it was not influenced

by the intravenous injection of 1 mg. of atropine sulphate, but that it was relieved by emptying the stomach and also by neutralizing the free acidity. The patient could be kept free from distress by maintaining continuous neutralization of the free acidity. Agonizing pain was pro-

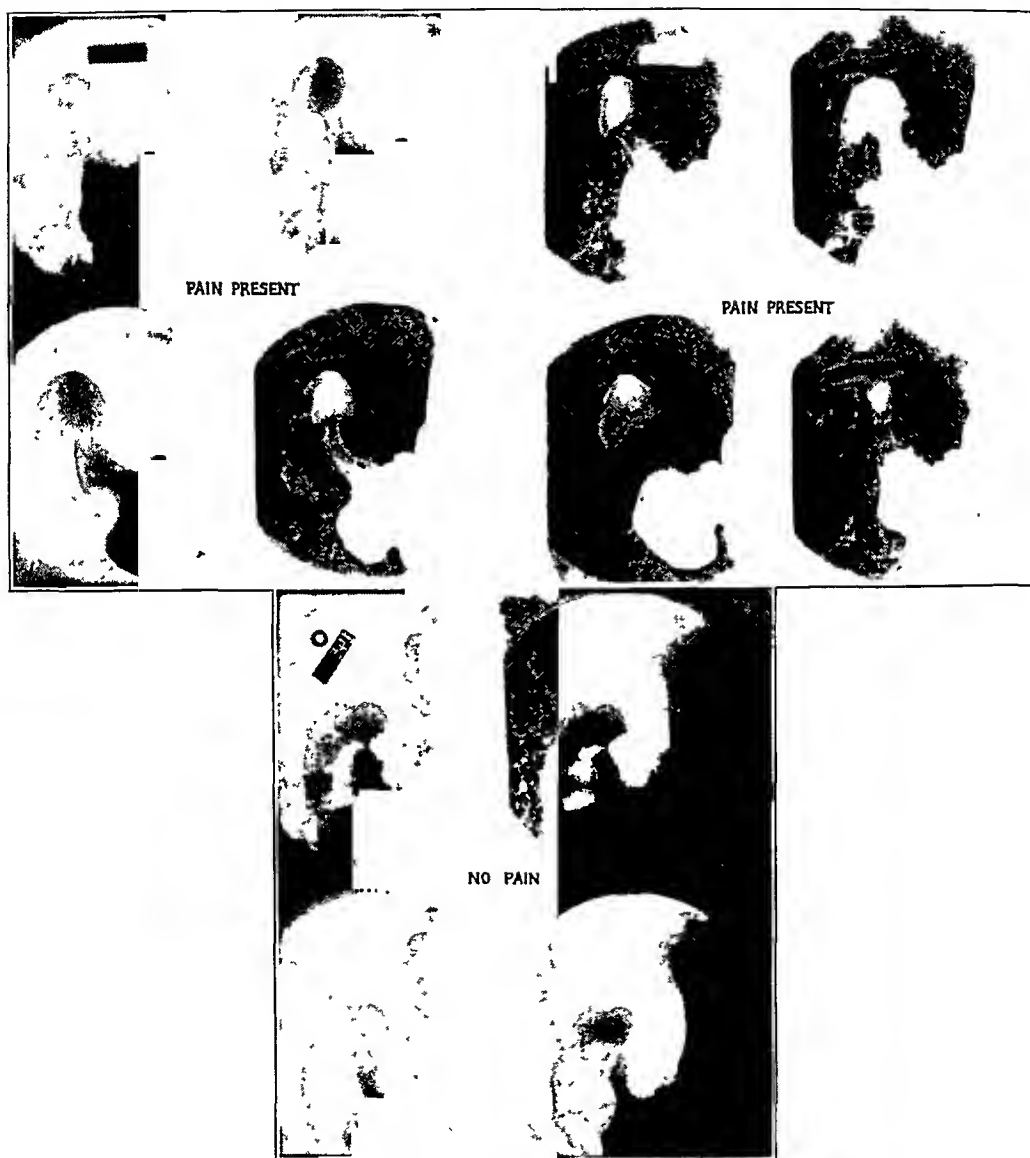


Fig. 6.—Roentgenograms made in a case of carcinomatous gastric ulcer.

duced by the injection into the stomach of the normal physiologic irritant, *the patient's own gastric juice*, or also by increasing the amount of gastric secretion by means of the injection of histamine hydrochloride.

The kymographic method as employed in our experiments provides a record of intragastric tension and therefore of gastric tonus as well as gastric motility, but it does not provide information with regard to the pylorus or the duodenal bulb. These regions were studied care-

fully roentgenologically¹³ in 1926, as has been mentioned, and evidence was obtained that ulcer pain is not due to pylorospasm, spasm of the gastric antrum or increased pressure in the antrum. However, in view of the criticism of Hurst^{28b} further observations were made.

The roentgenologic appearance of the stomach in the presence of pain and again in its absence in a case of benign gastric ulcer is illustrated in figure 5. The second series of exposures was made thirty minutes after the first, and at a time when the pain had disappeared as the result of the administration of an alkali. Fluoroscopic studies of the stomach during the presence of pain following the administration of a preparation of barium sulphate made up in a 0.5 per cent solution of hydrochloric acid corroborated the roentgenologic findings reproduced here. The stomach emptied well during pain, thus proving that the pain was not due to pylorospasm. There was no spasm in the gastric antrum, in the body of the stomach or in the duodenal bulb.

Similar observations made in the case of carcinomatous gastric ulcer previously mentioned are presented in the series of roentgenograms shown in figure 6, illustrating and confirming the fluoroscopic studies. The ulcer crater on the lesser curvature may be noted. The prepyloric deformity was present constantly, regardless of the acidity of the gastric content and regardless of the presence or absence of pain. It varied somewhat in its configuration with different phases of filling, but this variation was independent of any variation in the pain, as may be seen from a study of the illustration. Eight exposures of the antrum were taken during the presence of pain induced by the administration of acid solution of barium sulphate and four more thirty or forty minutes later after the pain had been relieved by alkali medication. In some the antrum is well filled out; in others, it is almost empty. The pylorus is open in nearly all and the duodenal bulb well filled. The same variations occur regardless of the presence or absence of pain. The patient was operated on and a partial gastrectomy performed. Gross and microscopic examination of the gastric antrum revealed diffuse carcinomatous infiltration throughout the lymphatic vessels of the submucosa with marked thickening and rigidity of the tissue. The constant prepyloric deformity noted roentgenologically was thus attributable to anatomic change rather than to spasm. In these observations it is quite clear that the pain was not due to spasm of the body of the stomach, of the antrum, of the pylorus or of the duodenal bulb, and there is no evidence of a constricting wave of gastric peristalsis which might have produced an increase in the intragastric tension in the pyloric segment not transmitted to the main segment, as suggested by Hurst.

COMMENT

A complete discussion of the subject of visceral pain can scarcely be attempted in this paper. The reader is undoubtedly familiar with the

original work of Lennander,⁴⁵ Ross,⁵¹ Mackenzie,⁵² Hurst⁹ and others. Of the numerous studies on this subject in recent years those of Soma Weiss and Davis,⁵³ Pratt, Golden and Rosenthal,⁵⁴ Rudolf and Smith,⁵⁵ Davis, Pollock and Stone⁵⁶ and particularly the monographs of Lemaire,⁵⁷ Morley⁴⁶ and Capps⁵⁸ are of great interest. In our work, however, ulcer pain has been accepted as a fact. The lesion is known to be present; the nerve supply is abundant; and in some way an adequate stimulus is applied to some nerve mechanism with consequent perception of pain. In this study our attention has been centered on the manner in which pain arises, on its site of origin, and on the nature of the adequate stimulus, rather than on the type of nerve or nerve ending excited, the pathway of the pain or the manner in which it is referred.

The Source of Ulcer Pain.—In view of the many and contradictory theories which have been advanced to explain ulcer pain, it is important to determine first, if possible, the site of origin of the pain. Does it arise in or adjacent to the ulcer itself or in some more distant part of the stomach or duodenum? Hurst,^{28a} Smith, Paul and Fowler²⁹ and others have considered the source to be the normal tissue of the wall of the pyloric antrum and the adequate stimulus the increased tension resulting from increased intragastric pressure. Ginsburg, Tumpkowsky and Hamburger,¹⁴ Carlson¹⁵ and Christensen,³⁶ on the other hand, while agreeing that the site of origin is the normal musculature, have considered peristalsis to be the adequate stimulus. The difference between the pain of ulcer and the "hunger pang" of a normal stomach was attributed apparently to the hypersensitivity of the whole region induced in the former instance by the more or less distant inflammatory lesion. A careful consideration of all the evidence, however, indicates

51. Ross, James: On the Segmental Distribution of Sensory Disorders, *Brain* **10**:333, 1888.

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53. Weiss, Soma, and Davis, David: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, *Am. J. M. Sc.* **176**:517, 1928.

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55. Rudolf, R. D., and Smith, A. G.: Observations on Visceral Pain, *Tr. A. Am. Physicians* **45**:264, 1930.

56. Davis, Loyal; Pollock, L. J., and Stone, T. T.: Visceral Pain, *Surg., Gynec. & Obst.* **55**:418 (Oct.) 1932.

57. Lemaire, A.: Le problème de la sensibilité viscérale et l'anesthésie de splanchnalgies, Paris, Presses Universitaires de France, 1928.

58. Capps, J. A., and Coleman, George H.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium, and Peritoneum, New York, The Macmillan Company, 1932.

that ulcer pain arises at the site of the ulcer. Our studies have shown that ordinarily ulcer pain is entirely independent of gastric peristalsis, gastric tone, intragastric pressure and pylorospasm, except as these influence gastric emptying and thereby affect the chemical nature of the fluid bathing the surface of the ulcer itself. In those cases in which the pain is intermittent or remittent, the waves of pain corresponding with the waves of peristalsis noted kymographically, it seems probable that here also the pain is not due to changes in the tension of the muscles in the normal stomach but rather to direct mechanical irritation of the lesion itself either by a transmitted tug or by the further advance of the contraction to the site of the ulcer. The direct observations of Dragstedt and Palmer,⁴⁹ in the patient operated on under local anesthesia as described, have shown that direct irritation of a sufficiently sensitive ulcer, such as may result from touching, rubbing, pinching, applying acid to the surface and circular muscular spasm, is extremely painful, whereas peristalsis and the application of similar trauma to other parts of the stomach are painless. It seems necessary to conclude, therefore, that *ulcer pain arises at the site of the lesion*.

Ulcer Sensitivity.—Before considering the phenomenon of ulcer sensitivity or irritability in detail, it seems advisable to review our knowledge of the etiology and pathogenesis of ulcer, giving particular attention to the rôle of acid gastric juice. Alvarez⁵⁹ recently published an excellent résumé of the subject with an extensive bibliography.

In 1926, the literature dealing with the alleged incidence of peptic ulcer associated with complete achlorhydria was reviewed⁶⁰ with the conclusion that there were no well documented cases on record. Many of the older writers had accepted a single Ewald or a single fractional test meal as satisfactory evidence of the inability of the stomach to secrete free hydrochloric acid. It was shown, however, that several analyses must be made before a diagnosis of achlorhydria can be considered as established. Achlorhydria proved by a test with histamine is usually accepted as satisfactory, but recently the conclusive value of this test has been properly questioned by Gaither,⁶¹ Comfort and Osterberg⁶² and Klumpp and Bowie.⁶³ We have also noted instances in which a test with histamine was reported as showing no free acid,

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60. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria, *Arch. Int. Med.* **38**:603 (Nov.) 1926.

61. Gaither, E. H.: Diagnostic Value of Secretory Function in Gastric Disease: Various Methods Studied and Compared, *Ann. Int. Med.* **5**:992, 1932.

62. Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine, *J. A. M. A.* **97**:1141 (Oct. 17) 1931.

63. Klumpp, T. G., and Bowie, M. A.: Studies on Gastric Secretion, *J. Clin. Investigation* **12**:1 (Jan.) 1933.

whereas a second test showed its presence in normal quantity. Neither conclusive nor even fairly acceptable evidence, therefore, of the presence of complete achlorhydria in typical chronic ulcer has yet been reported. Berg ^{64a} referred to a case of duodenal ulcer and achlorhydria following gastro-enterostomy, but did not give the evidence. Gutzeit ^{31b} stated that he found a gastric ulcer by gastroscopic examination in a patient with pernicious anemia and achylia proved by a test with histamine, but the lesion was seen only once and the patient had no symptoms of ulcer.⁶⁵ Hurst ^{28c} made the statement, "There is thus no evidence that an ulcer ever develops in the stomach or duodenum in the absence of free hydrochloric acid." This is extremely significant, for Vanzant, Alvarez, Eustermann, Dunn and Berkson,⁶⁶ in their extensive studies on gastric secretion, found true achlorhydria present in 10.8 per cent of males of all ages above 25, and in 13.8 per cent of all females above 20. These results are quite in accord with the 13 per cent incidence of anacidity reported by Lerman, Pierce and Brogan.⁶⁷ *If free hydrochloric acid plays no rôle in the genesis of ulcer, the incidence of achlorhydria in ulcer should be from 10 to 13 per cent instead of 0.*

It is furthermore highly significant that ulcer occurs only in those portions of the gastro-intestinal tract exposed to peptic activity: the lower part of the esophagus, the stomach and the proximal portion of the duodenum. Following operative procedures which bring the jejunum into contact with unneutralized acid, lesions may develop in the jejunum, or if the anastomosis is lower, in the ileum or colon.

The ulcers of Meckel's diverticulum, studied carefully by Aschner and Karelitz,⁶⁸ Lindau and Wulff,⁶⁹ Matthews and Dragstedt⁷⁰ and others are extremely important. These lesions occur in the intestinal mucosa lining the neck of the diverticulum, and are associated with the presence in the sac of gastric mucosa secreting free hydrochloric acid. The experimental production of these lesions by Dragstedt and Matthews,⁷⁰ to be mentioned again later, is a conclusive demonstration of the rôle of hydrochloric acid in the pathogenesis of these ulcers.

64. (a) Berg, H. H.: Roentgenuntersuchungen am Innenrelief des Verdauungskanaals, ed. 2, Leipzig, Georg Thieme, 1931, p. 149; (b) *ibid.*, p. 321.

65. Gutzeit, Kurt: Personal communication to the authors.

66. Vanzant, F. R.; Alvarez, W. C.; Eustermann, G. B.; Dunn, H. L., and Berkson, Joseph: The Normal Range of Gastric Acidity from Youth to Old Age, *Arch. Int. Med.* **49**:345 (March) 1932.

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69. Lindau, Arvid, and Wulff, Helge: The Peptic Genesis of Gastric and Duodenal Ulcer: Especially in the Light of Ulcers in Meckel's Diverticulum and the Post-Operative Ulcers in the Jejunum, *Surg., Gynec. & Obst.* **53**:621, 1931.

70. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265, 1932.

Pathologically, the work of Moskowitz,⁷¹ Konjetzny,⁷² Puhl,⁷³ Aschner and Grossman⁷⁴ and others has quite altered the time-honored concept of the pathogenesis of ulcer. It has been shown by these workers that gastritis and duodenitis are constantly associated with ulcer, and that occasionally they alone may produce the ulcer syndrome. Various stages of transition from gastritis to ulcer have been demonstrated. Konjetzny and Puhl favor the view that the same inciting agent is present in both of these lesions. They believe that it is a toxic or infectious process and deny the rôle of gastric acidity.

Büchner⁷⁵ and his pupils, on the other hand, while confirming the work of Konjetzny as regards the relationship between gastritis and ulcer, present evidence that both are of peptic origin. The layer of "fibrinoid necrosis" described by Askanazy⁷⁶ and invariably present in ulcer is considered by Büchner as the typical picture of corrosive necrosis. The small lesions of Konjetzny's ulcerative gastritis have been shown by Büchner to have a similar histologic structure. Furthermore, Büchner and his pupils have succeeded in producing this picture of ulcerative gastritis experimentally in cats by the injection of acid into the stomach, and also in rats by stimulation of gastric secretion with histamine during periods of fasting. In the latter experiments there were produced not only the erosions and the small, although grossly visible, lesions of ulcerative gastritis, but small ulcers of the prosthoma extending occasionally to the muscularis propria. A somewhat similar observation was reported by Silbermann,⁷⁷ who noted the erosions of ulcerative gastritis in the stomach of dogs following sham feeding experiments. This work was confirmed by Büchner and attributed to the effect of undiluted and unneutralized acid on the mucosa.

The first satisfactory production of ulcer in a sense was that inadvertently obtained by surgeons in human material by various types

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of gastro-enterostomy with ligation or resection of the pylorus. The incidence of jejunal ulcer following this procedure was high.^{28d} In 1923, Mann and Williamson⁷⁸ found experimentally that transplantation of the bile and pancreatic ducts to the terminal ileum in the dog resulted in the formation of ulcers in nearly all of the animals. This observation has been abundantly repeated and confirmed, in various types of so-called "duodenal drainage operations," by Morton,⁷⁹ McCann,⁸⁰ Matthews and Dragstedt,⁷⁰ Gallagher and Palmer⁸¹ and others. Similarly, it has been observed that complete biliary obstruction results experimentally in the formation of ulcers in about 60 per cent of the animals, as stated by Berg and Jobling,⁸² Bollman and Mann⁸³ and Kim and Ivy.⁸⁴ Elman and Hartmann⁸⁵ reported the formation of ulcers in six dogs in which the pancreatic juice was drained away for thirteen days or more, but Owings and Smith⁸⁶ and Berg and Zucker⁸⁷ were unable to confirm this observation. Dragstedt,⁸⁸ however, in his extensive studies on dogs with total pancreatic fistulas has found it very difficult to keep animals alive for more than a week because of the rapidity with which duodenal ulcers arise, perforate and cause death from peritonitis. When such animals are fed alkali regularly, it is possible to prevent the formation of ulcers for as long as six months. Apparently any disturbance of the normal mechanism for the neutralization of acid in the duodenum will result in the formation of ulcers in a very high percentage of the experiments. The lesions, frequently hemorrhage, invade adjacent organs and

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87. Berg, B. W., and Zucker, T. F.: Comparative Frequency of Peptic Ulcers After Deprivation of Bile and Pancreatic Juice, *Proc. Soc. Exper. Biol. & Med.* **30**:330 (Dec.) 1932.

88. Dragstedt, L. R.: Personal communication to the authors.

often perforate with resulting death from peritonitis. They are not thrombotic or infarctive in origin, for Mann has shown conclusively that the process is an invasive one; that it begins in the mucosa and extends into the deeper layers and thus increases in size. It should be noted here, as pointed out by Büchner,⁸⁹ that in human material also the ulcerative lesion may *invade* adjacent organs—a process which cannot be explained by thrombosis or embolism with subsequent infarction. The acid genesis of these ulcers is perhaps most conclusively proved by the experimental production of ulcers of Meckel's diverticulum by Matthews and Dragstedt.⁹⁰ Here the acid gastric juice draining from a Pavlov pouch into a loop of ileum results in the formation of ulcers. Continued neutralization of the acid allows the lesions to heal and prevents the formation of new ones.⁹⁰ *These experiments show clearly that unneutralized gastric juice is able to initiate in normal living tissue a localized ulcerative process and that it is also able to bring about the extension and chronicity of the lesion so induced.*

In view of the foregoing clinical, pathologic and experimental considerations, it is apparent that peptic ulcer occurs only in association with acid gastric juice, that the various stages from ulcerative gastritis to the formation of callous ulcer have been described anatomically, that all of these stages have been reproduced experimentally by various methods which increase the exposure of the mucosa to acid gastric chyme, and that in normal tissue acid gastric juice alone is able to initiate, maintain and extend an ulcer. This brings us, then, to a consideration of the process which renders an ulcer sensitive to otherwise inadequate stimuli. There is evidence that this is due to the inflammatory process itself, even though Singer and Palmer⁹¹ were unable to establish a relationship between the various degrees of inflammation and the sensitivity of ulcers. This may have been due in part to inability to find a satisfactory means of measuring degrees of inflammation.

The clinical evidence of such a relationship is quite definite. The first symptomatic signs of subsidence of the inflammatory process and therefore of healing should be and are a cessation of spontaneous distress followed by failure of the previously adequate stimuli to produce pain. During the first few days of antacid ulcer therapy, and also during the early days of a spontaneous remission, during which time the reparative healing processes are apparently in ascendancy, the sensitivity to acid more or less rapidly diminishes, more *time* is required for the production of pain, and the resulting pain becomes less and less severe.⁹²

89. Büchner,⁷⁵ p. 4.

90. Matthews, W. B.: Personal communication to the authors.

91. Singer, Harry, and Palmer, W. L.: Unpublished observations.

92. Palmer, W. L.: The Value of Acid Neutralization in the Treatment of Gastric and Duodenal Ulcers, Arch. Int. Med. **46**:165 (Aug.) 1930.

Coincidentally the epigastric soreness and the rigidity of the rectus muscle disappear. Berg ^{64b} has shown roentgenologically that these phenomena occur long before the ulcer crater closes. We have found that in these stages of partial to complete healing, the lesion is insensitive to acid and furthermore desensitization occurs more rapidly on an antacid than on an acid-producing regimen.⁹² These are the results to be expected, if acid gastric juice is responsible, as has been suggested, for the initiation and continuation of the lesion, because prolonged neutralization of the acid should allow granulation tissue to fill in, mucosal cells to bridge the gap, and the ulcer to heal.

Further evidence that the enhanced irritability of the ulcer is due to the continued action of the noxious agent, acid gastric juice, is to be found in a case of gastric carcinoma previously described.^{13c} In this instance, free hydrochloric acid was present in normal amounts. The spontaneous pain was severe; it could be produced in almost agonizing form by the "acid test," and it was completely relieved by antacid ulcer management (the usual Sippy regimen). With the continuation of treatment, not only did the patient remain free from spontaneous distress, but the "acid test" gradually became negative also, giving proof of the transformation from an acid-sensitive to an acid-insensitive lesion. The desensitization of the pain-producing mechanism seemed to result directly from the continued neutralization of the free acidity. This neutralization presumably protected the carcinoma from the digestive action of the gastric juice and thereby preserved over the surface of the lesion a sufficient layer of necrotic tissue to protect the mechanism of pain from the irritating effect of the acid used in the "acid test." This same phenomenon was observed in the case of carcinomatous gastric ulcer described in detail in the present paper. These observations are important because they constitute further evidence not only that acid gastric juice may destroy living tissue, but that it may, in the lesion produced, so lower the pain threshold that normally subthreshold stimuli become painful.

The importance of acid sensitization in ulcer was also clearly shown in the original studies ^{13d} of a case of gastrojejunal ulcer. In this instance gastric peristalsis was powerful but painless until an hour after the injection of 1.5 mg. of histamine hydrochloride subcutaneously. This produced a large volume of highly acid gastric secretion (free acidity of 100) which, in *time*, increased the irritability of both the motor and the sensory mechanisms of the stomach. Remittent pain appeared, the most intense pains corresponding with the peak of the gastric contractions, which had then increased in intensity. With continued neutralization of the free acidity, however, the pain gradually decreased and disappeared entirely even though the powerful peristaltic waves persisted.

It may be seen that this theory of sensitization as due to the continued destructive action of acid gastric juice is quite in accord with our concept of the etiology of ulcer. Free hydrochloric acid is responsible for the initiation and continuation of the inflammatory process and for the enhanced irritability of the tissue. When the lesion is protected from the destructive effect of the acid, the sensitivity disappears quickly, pain ceases, tenderness and rigidity disappear, and the ulcer heals.

The Adequate Stimulus.—Given a sensitive lesion, the production of pain depends on the presence of an adequate stimulus. It has been shown that this may be either mechanical or chemical. The early observations of Ginsburg, Tumpowsky and Hamburger¹⁴ and of Carlson¹⁵ showed definitely that under proper conditions gastric peristalsis itself may produce pain. Our own kymographic studies have been confirmatory. Dragstedt and Palmer⁴⁹ observed that direct mechanical irritation of an acutely inflamed ulcer, as by rubbing or pinching or local muscular contraction, produced severe pain. There can be no doubt, therefore, that purely mechanical stimuli may be entirely adequate. In the case of benign lesions, however, there is no evidence at present that an ulcer can occur and be sufficiently sensitive for the production of pain by mechanical stimulation without previous acid sensitization. With malignant lesions, on the other hand, the advance of the process is not dependent on continued peptic activity, and consequently enhanced irritability of the tissue may occur without the presence of free hydrochloric acid, as in the cases of gastric carcinoma with pain associated with a complete absence of free hydrochloric acid.^{13e}

The evidence that free hydrochloric acid may be an adequate stimulus to the pain-producing mechanism may be summarized as follows:

1. When pain is present, a high degree of free hydrochloric acid is practically always found in the stomach.

2. The pain is relieved by emptying the stomach or by any measure which results in the neutralization of the gastric free acidity.

3. The pain may be relieved by emptying the stomach, and be made to reappear by reinjecting the acid chyme whereas the injection of gastric content in which the free acidity has been neutralized is not productive of pain.

4. Ulcer pain, typical in kind, location and severity, may be induced under suitable conditions by the injection into the stomach of dilute solutions of hydrochloric acid in perfectly physiologic concentrations (from 0.2 to 0.3 per cent). Dilute solutions of other acids and alkalis (tenth-normal solution of sodium hydroxide) have also evoked pain in highly sensitive lesions.

5. Ulcer pain may be induced by the injection of acid gastric juice from another patient or by stimulation of the patient's own gastric secretion by histamine.

6. In one instance, pain was produced by direct application of acid to the surface of the ulcer.⁴⁹

It is impossible to estimate the relative rôles of these two forms of stimuli in the production of the usual ulcer pain. The acid factor must be present if pain is to ensue. On the other hand, an ulcer is seldom free from the effect of mechanical forces. It is significant, however, that a mechanical factor was demonstrated in Palmer's original work only in those cases in which the pain was wavelike, remittent or intermittent (9.5 per cent of the observations). Clinically, the most frequently encountered type of distress is not wavelike, but steady and continuous, just as is that usually seen following the introduction of acid into the stomach. Beams³⁸ noted, however, following the administration of amyl nitrite, temporary, almost transitory, relief from pain in twelve of twenty cases of duodenal ulcer and in six of ten cases of gastric ulcer, accompanied by a brief cessation of peristalsis and decrease in gastric tone. These observations apparently show that a sudden profound relaxation of the musculature may cause a brief respite from pain and suggest that frequently a combination of the mechanical and chemical forms of stimuli may be present—a summation effect.

The Effect of Antispasmodics.—The relief from spontaneous pain resulting from the injection of atropine sulphate has been attributed to an antispasmodic effect (Smith, Paul and Fowler²⁰). While this possibility cannot be completely denied, our experiments suggest another explanation, for under certain conditions, atropine sulphate does not relieve the pain, and pain may be induced after atropinization by the introduction of acid into the stomach. The intravenous administration of atropine sulphate has two striking effects on the stomach: It stops motility temporarily and it inhibits secretion. The immediate result of the former is an abrupt cessation of gastric emptying. A rational hypothesis is that the alkaline duodenal content then bathes the surface of the ulcer, located in the duodenum, and stops the pain. We are not acquainted with any instances in which atropine sulphate has stopped the pain of gastric ulcer. Calcium chloride apparently acts in a similar manner, although it not only checks active peristalsis but also seems to induce reverse peristalsis, as is indicated by the marked nausea and occasional emesis noted. It is also quite likely that the marked peripheral vasodilation may have a transitory ameliorative effect on pain, regardless of its origin. The careful studies of Beams³⁸ on the effect of nitrites on ulcer pain have not been repeated by us. The brief but definite relief from pain noted by him in certain cases of gastric as well as duodenal ulcer cannot be explained on the basis of cessation of gastric emptying or reverse peristalsis. It is possible that the concomitant distracting subjective symptoms produced by the nitrites due to the peripheral vasodilation may have played an important rôle in the relief,

but, on the other hand, it is also quite possible that the sudden antispasmodic effect of the drug may have been sufficient to induce temporary relief. There were instances in the experiments of Beams in which the pain continued unrelieved by the nitrites just as it did in some of our experiments with calcium chloride.

Production of the Mechanism of Pain.—It has been seen that an irritable pain mechanism may be made to respond by the application of an adequate stimulus, mechanical or chemical. We have not yet considered the manner in which the stimulus affects the mechanism, how it produces pain. Meyer, Fetter and Strauss⁴¹ ascribed the pain to ischemia and asphyxia due to depletion of the vascular bed in and about the ulcerous area, but Dragstedt and Palmer⁴⁰ noted that touching of the hyperemic serosa above the ulcer evoked pain without producing any vascular disturbance, and that the application of acid also produced pain without any discernible effect on the blood supply. The very painful circular spasm, on the other hand, was accompanied by a blanching of the contracted area. This is the normal effect of contraction in the bowel, and cannot be considered in itself as the cause of the pain. It may be noted further that Beams in his studies of the effect of nitrites on ulcer pain found no evidence of muscular spasm about the lesion, for the deformities in the stomach or intestine were not decreased by the nitrite, but were increased, the deformity being accentuated when the uninvolved portion of the stomach or intestine relaxed. Ivy,⁴⁵ according to Alvarez, suggested that the continuous type of distress might be due to congestion, edema and inflammatory reactions about the ulcer, all of which lower the threshold for stimuli, and that the intermittent type of pain might be due to changes in the tonicity of the muscle at the site of the ulcer, brought about by peristalsis or local spasm. Kinsella⁴⁷ considers the pain to be due to increased tension within the wall of the bowel, "congestion in indurated tissue aggravated by functional hyperemia." We are more inclined to regard increased tension in the tissues as a part of the inflammatory process and, as such, as partially responsible for the increased irritability and sensitivity. It therefore plays only an indirect rôle in the production of pain, although it is conceivable that when sufficiently acute, it alone may constitute an adequate stimulus.

The mechanical stimuli, usually due to peristaltic traction or localized muscular spasm, apparently act directly and mechanically on tissue whose sensitivity has been enhanced by the inflammatory process.⁴⁹ The action of chemical irritants is not so obvious. Three possibilities were postulated originally:¹³ edema, localized muscular spasm and a direct effect on the nerve endings. It was stated at that time:

The instantaneous production of severe pain which results at times in very sensitive ulcers from the injection of acid does not argue for the etiologic relationship of gross tissue edema to pain. Certain other characteristics of the pain make

it difficult to conceive of its being due to localized muscle spasm. It may come on gradually, being scarcely noticeable at first, and then, by almost imperceptible gradations increase in severity to intense pain. It disappears in a similar manner. As the sensitiveness of the pain-producing mechanism decreases, the latent period increases, the severity of the pain diminishes, and the pain threshold rises. This occurs in both benign and malignant ulcers. In benign ulcers, this decrease in the sensitiveness of the pain-producing mechanism seems to be related definitely to the healing process. Carcinomas can scarcely be said to heal, but the methods which desensitize a carcinoma are those which check peptic activity, prevent digestion of the slough and of poorly vitalized tissue, and thereby presumably protect the sensitive mechanism from the action of the chemical irritant. To me, these phenomena seem to suggest that the acid may act by direct irritation of exposed nerve endings rather than by the production of localized muscle spasm.

The evidence offered in the present paper seems to us to give further support to this view. The irritability or sensitivity of the tissue is so enhanced by the inflammatory process that the acid, acting on the tissue—probably directly on exposed nerve endings—becomes an adequate stimulus for the production of pain.

CONCLUSIONS

1. Ulcer pain arises at the site of the lesion.
2. It is not directly dependent on pylorospasm, gastric motility or intragastric pressure.
3. It depends on the presence of an adequate stimulus acting on an irritable pain-producing mechanism located in or adjacent to the lesion itself.
4. The enhanced irritability of the tissue in or about the lesion is dependent on the presence and continued action of acid gastric juice; conversely, desensitization may be produced by continued neutralization.
5. The *adequate* stimulus may be either (*a*) mechanical, due to peristaltic traction or local spasm; or (*b*) chemical, due to the acid reaction of the chyme.
6. The *usual* stimulus is the free hydrochloric acid of the gastric content.
7. The action of the stimulus, be it mechanical or chemical, is probably exerted directly on nerves rendered hyperirritable by inflammation resulting from the destructive effect of acid gastric juice.

PLASMOCHIN, PLASMOCHIN WITH QUININE SALTS AND ATABRINE IN MALARIA THERAPY

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The synthetic drug plasmochin, sometimes spelled plasmoquine, was developed in 1915. It is said to be (6 methoxy 8 α methyl δ diethylamino butyl) aminoquinoline. Thus, although it contains quinoline, it is not synthetic quinine.

At first this synthetic remedy was sold as plasmochin simplex. Later, quinine was added to it, and the combined product was called plasmochin compound. Finally, a larger percentage of quinine was added, and the mixture was sold as plasmochin with quinine salts. The latter has also been called quinoplasmoquine. At one time it was called beprochin.

Plasmochin is sold in the following forms:

1. Plasmochin simplex or plain: A salt of plasmochin, which is usually sold in bottles of twenty-five tablets, each tablet containing the equivalent of 0.02 Gm., or $\frac{1}{3}$ grain, of plasmochin hydrochloride.

2. Plasmochin compound: Usually marketed in bottles of fifty tablets. Each tablet contains the equivalent of 0.01 Gm., or $\frac{1}{6}$ grain, of plasmochin hydrochloride, combined with 0.125 Gm., or 2 grains, of quinine sulphate.

3. Plasmochin with quinine salts: Usually supplied in bottles of one hundred tablets. Each tablet contains the equivalent of 0.01 Gm., or $\frac{1}{6}$ grain, of plasmochin hydrochloride, with 0.3 Gm., or $4\frac{1}{2}$ grains, of quinine sulphate.

Recently a drug called atabrine has been marketed. This synthetic antimalarial substance is based on a heterocyclic system different from that of plasmochin. It is said by the manufacturers to be the dihydrochloride of 2 methoxy 6 chlor 9 (α methyl δ diethylamino butyl) amino-acridine, and at first it was called erion.

LABORATORY EXPERIMENTS

1. *Plasmochin and Plasmochin with Quinine Salts.*—Numerous laboratory studies with plasmochin have been reported since Roehl's

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original experiments,¹ especially those of Hegner and Manwell,² Manwell,³ Wampler,⁴ Fournneau and his associates et al.⁵ and myself.^{6a, b}

Several facts are apparent from these studies, in all of which canaries were used as experimental material. In the first place, plasmochin is definitely more effective than quinine against avian malarias. Roehl found plasmochin about sixty times more potent than quinine. Manwell stated that plasmochin was uniformly superior to quinine in the treatment of avian malaria. In a series of controlled experiments I^{6c} found that in a canary which had received an experimental inoculation of *Plasmodium cathemerium* by needle, infection could invariably be prevented by intramuscular injections of plasmochin simplex in daily doses as small as 0.00016 Gm., provided the bird had received at least one dose of plasmochin subsequent to receiving the infective inoculum. This was a therapeutic rather than a prophylactic effect. Daily intramuscular injections of 0.0005 Gm. of quinine dihydrochloride did not protect the birds against infection from similar inoculations. The amounts of plasmochin and quinine used were maximal subtoxic doses for canaries which averaged 15 Gm. in weight.

The various avian malarias have been found to react differently to plasmochin. Manwell³ noted that, although plasmochin was more effective than quinine in treating avian malaria, this superiority differed in degree according to the species of plasmodium.

Tests of the action of plasmochin on parasites of avian malaria in vitro were made by Manwell^{3b} and by Nono and myself.⁷ Manwell

1. Roehl, W.: Die Wirkung des Plasmochins auf die Vogelmalaria, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:11, 1926; Naturwissenschaften **14**:1156, 1926.

2. Hegner, R., and Manwell, R. D.: The Effects of Plasmochin on Bird Malaria, Am. J. Trop. Med. **7**:279, 1927.

3. Manwell, R. D.: (a) Further Studies on the Effect of Quinine and Plasmochin on the Avian Malarias, Am. J. Trop. Med. **10**:379, 1930; (b) Quinine and Plasmochin Therapy in *Plasmodium Rouxi* Infections, with Further Notes on the Effects of These Drugs on the Other Avian Malarias, *ibid.* **12**:123, 1932.

4. Wampler, F. J.: A Preliminary Report on the Early Effects of Plasmochin on *Plasmodium Cathemerium*, Arch. f. Protistenk. **69**:1, 1930.

5. Fournneau, E.; Tréfouel, J., and Tréfouel, J. (Mme.); Stéfanopoulo, G., and Others: Contribution à la chimiothérapie du paludisme: Essais sur la malaria des canaris, Ann. Inst. Pasteur **44**:503, 1930.

6. Russell, P. F.: (a) Avian Malaria Studies: II. Prophylactic Plasmochin Versus Prophylactic Quinine in Inoculated Avian Malaria, Philippine J. Sc. **46**:347, 1931; (b) Plasmochin Simplex, a Prophylactic Drug in Avian Malaria, Am. J. Trop. Med. **11**:279, 1931; (c) Avian Malaria Studies: I. Prophylactic Plasmochin in Inoculated Avian Malaria, Philippine J. Sc. **46**:305, 1931.

7. Russell, P. F., and Nono, A. M.: Avian Malaria Studies: VII. Plasmochin as a Prophylactic Drug in Sporozoite Infections of Avian Malaria, Philippine J. Sc. **49**:595, 1932.

found that plasmochin had little effect on the infective qualities of *Plasmodium elongatum* unless it was allowed to act for six hours or more. On the other hand, Nono and I, working with *Plasmodium capistrani*, obtained results which indicated that plasmochin inactivated or devitalized asexual forms of the parasite (not sporozoites) when allowed to remain in contact with them in vitro for fifteen minutes.

The combination of plasmochin and quinine sold as plasmochin with quinine salts appears to be more effective against avian malaria than either quinine or plasmochin alone. For example, in a series of hitherto unpublished experiments I was able to sterilize the blood of each of six infected canaries by giving them daily intramuscular injections of plasmochin with quinine salts for a week. Each injection contained 0.00005 Gm. of plasmochin and 0.0015 Gm. of quinine hydrochloride. The parasite in this instance was *Plasmodium capistrani*, and injections were begun two weeks after a typical acute malarial attack. Sterilization of the blood was proved by injection into normal birds, with negative results, and by reinfection with the same strain of *Plasmodium capistrani*. In two other series of unpublished experiments I was unable to sterilize the blood of similarly infected canaries by similarly administered injections of quinine or of plasmochin simplex. The daily dose of quinine dihydrochloride was 0.0005 Gm.; that of plasmochin simplex was 0.0002 Gm. Plasmochin simplex at first appeared to produce the same results as plasmochin with quinine salts; in each case there was complete disappearance of parasites from the blood smears examined for thirty minutes. But in every instance a residual infection was present, as was shown by subsequent transference of the blood to uninfected birds and by the eventual reappearance of parasites in the blood smears of the birds which had received the drugs.

Manwell^{3b} worked with *Plasmodium praecox* and *Plasmodium cathe-merium* and administered plasmochin and quinine orally instead of intramuscularly. He reported that a combination of the drugs had only a slight if, indeed, any advantage over either drug administered alone. He also found wide differences in the susceptibility of individual birds to treatment. He interpreted this fact as indicating that the effect of plasmochin was exerted indirectly "through a stimulation of some sort to the natural defensive powers of the host, as well as directly upon the parasite." The fact that my results following intramuscular injection of the drug were more uniform than Manwell's³ following oral administration may indicate that variation in response to treatment by mouth is due to differences in absorption of the drug rather than to any other cause.

Other laboratory experiments of interest are those of Epstein,⁸ who tested the effect of plasmochin on the uterine muscle of cats and guinea-pigs in two ways: in situ in living animals, and when the muscle was excised and resting in a physiologic solution. On administering the drugs intravenously to cats, he found that definite uterine contractions were caused by quinine in doses of 0.004 Gm. per kilogram of body weight. This corresponds roughly to about 4 grains (about 0.26 Gm.) for an adult human being and is thus within the therapeutic dose of quinine. It required 0.001 Gm. of plasmochin per kilogram of body weight to cause similar contractions. This dose corresponds to about 1 grain (about 0.06 Gm.) for an adult human being and is about three times the usual therapeutic dose. Epstein concluded that plasmochin is safer than quinine during pregnancy, if given in a therapeutic dose, but that in larger doses it has a definite effect on the uterus.

Eichholtz,⁹ experimenting with cats and rabbits, found that plasmochin in doses of more than 0.002 Gm. per kilogram of body weight, when administered intravenously, caused marked disturbance of the cardiac rhythm, but that this effect was of only short duration if the dose was reduced. When quinine was combined with plasmochin no arrhythmia occurred.

2. *Atabrine*.—Kikuth and his associates¹⁰ found that atabrine administered to infected birds in their laboratories showed a therapeutic index of 1:30 as compared with a similar index for plasmochin and an index of only 1:4 for quinine. In birds in which infection with *Plasmodium praecox* was at its height atabrine reduced the number of parasites in the peripheral blood, but, like plasmochin, it did not cause their complete disappearance. In parallel experiments quinine had no effect on the number of parasites. These investigators found atabrine to be a schizontocide, differing from plasmochin, which is essentially a gametocide.

In rabbits and cats the relative minimum lethal doses of atabrine, given orally, as compared with those of quinine and plasmochin, expressed in grams per kilogram of body weight, are as follows:

	Quinine	Plasmochin	Atabrine
Rabbits.....	0.5	0.022	0.4 to 0.5
Cats.....	0.005 to 0.007	0.1 to 0.15

PRACTICAL THERAPEUTIC USEFULNESS

The ideal antimalarial drug would be inexpensive, easy and pleasant to take, nontoxic and capable of bringing about rapid alleviation of

8. Epstein, D.: A Comparison of the Action of Plasmoquine and Quinine on the Uterus, *J. M. A. South Africa* 5:15, 1931.

9. Eichholtz, F.: Pharmacology of Plasmochin, *Beihefte z. Arch. f. Schiffsu. Tropen-Hyg.* 31:89, 1927.

10. Kikuth, W.; Sioli, F., and Peter, F. M.: (Atebrin) Zur Weiterentwicklung synthetisch dargestellter Malariamittel, *Deutsche med. Wchnschr.* 58:530, 1932.

symptoms and quick destruction of all forms of all species of the plasmodium, including sporozoites, wherever they are hidden in the body. Needless to say, there is no drug or combination of chemicals which meets these requirements. Quinine, in the usual doses, is easy to take, is nontoxic and rapidly alleviates symptoms, but it is expensive, is not pleasant to take and does not quickly destroy the parasites. It has no effect at all on the sporozoites, so far as has been determined.

It will be apparent, I believe, from this review, that plasmochin and atabrine are valuable available adjuncts to quinine, but it will also be clear that the ideal antimalarial drug is still to be found. Plasmochin and atabrine are easy and pleasant to take, and they rapidly alleviate symptoms, but they are expensive, they must be administered with special care lest a toxic dose be given, and they do not destroy all forms of the parasite quickly. Plasmochin is more effective against the sexual forms of the plasmodium than quinine, but it does not seem to have any direct effect on sporozoites. It should be emphasized that plasmochin and atabrine do not replace quinine; rather, they supplement it.

1. *Plasmochin and Plasmochin with Quinine Salts*.—It is not possible to review, in this article, all the clinical experiments with plasmochin which have been published since the early reports of Sioli,¹¹ Mühlens¹² and others. For example, a number of useful studies were made by members of the medical department of the United Fruit Company¹³ under the leadership of the late W. E. Deeks, who was quick to see the possibilities of plasmochin and plasmochin with quinine salts. So, too, Manson-Bahr,^{14a, b} Sinton and his collaborators,¹⁵ Hasselmann and

11. Sioli, F.: Prüfung des Plasmochins bei der Impfmalaria der Paralytiker, *Naturwissenschaften* **14**:1160, 1926; Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:319, 1926.

12. Mühlens, P.: Die Behandlung der natürlichen menschlichen Malaria-Infektion mit Plasmochin, Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg. **30**:25, 1926; *Naturwissenschaften* **14**:1162, 1926.

13. United Fruit Company, Medical Department, 15th to 20th Annual Rep., 1926-1931.

14. Manson-Bahr, P.: (a) The Action of Plasmochin on Malaria, *Proc. Roy. Soc. Med. (Sect. Trop. Dis.)* **20**:33, 1927; (b) Further Observations on the Effects of Plasmoquine and "Plasmoquine-Compound" on the Gametocytes of Benign Tertian and Subtertian Malaria, *Lancet* **1**:25, 1928; (c) The Therapeutic Effects of Plasmoquine in Pregnancy, *ibid.* **1**:882, 1932.

15. (a) Sinton, J. A.: Treatment of Malarial Fevers, *Tr. Seventh Cong. (1927) Far Eastern A. Trop. Med.* **2**:804, 1928; (b) Sinton, J. A., and Bird, W.: Studies in Malaria, with Special Reference to Treatment; Plasmoquine in the Treatment of Malaria, *Indian J. M. Research* **16**:159, 1928; (c) Sinton, J. A.; Smith, S., and Pottinger, D.: Studies in Malaria, with Special Reference to Treatment; Further Researches into Treatment of Chronic Benign Tertian Malaria with Plasmoquine and Quinine, *Indian J. M. Research* **17**:793, 1930.

Hasselmann-Kahlert,¹⁶ Amies,¹⁷ Kligler and Mer,¹⁸ Manifold,¹⁹ Schulemann²⁰ and many others have reported their clinical observations on the use of plasmochin alone or combined with quinine in the treatment of malaria.

At first, plasmochin alone was used, and, although there were some enthusiastic reports, it soon became evident that great care was required in administering this drug and that it was not always completely effective. Bass,²¹ whose experience with quinine in malaria therapy is unsurpassed, in 1930 compiled from published reports the following list of toxic symptoms observed after the use of plasmochin: cyanosis, pallor, nausea, gastric pain, headache, dizziness, epistaxis, weakness and hemoglobinuria. He gave the following conclusions: "Plasmochin has a definite effect on clinical malaria, and both clinical and parasitic cures may be accomplished with it alone. Plasmochin has far less effect on malaria than has quinine, and its toxicity, which is associated with methemoglobinuria, makes its routine use questionable."

It is now generally agreed that the only justifiable use of plasmochin simplex is in instances in which quinine is contraindicated, as at times in blackwater fever, in pregnancy or in the presence of idiosyncrasy. For adults the usual dose is one tablet after breakfast and another after the evening meal on the first day, one tablet after each of the usual three meals on the second to the seventh day and the same dose of three tablets on three successive days of each week thereafter until the parasites and symptoms have disappeared. For children up to the age of 5 years the dose is usually half a tablet once or twice a day; for those from 6 to 10 years of age the dose is half a tablet three or four times a day. If cyanosis appears, the drug should be discontinued for a few days.

Observations of the medical staff of the United Fruit Company,¹³ of Manson-Bahr^{14a, b} and of others showed that plasmochin in combination with quinine had stronger curative action and less toxic effect

16. Hasselmann, C. M., and Hasselmann-Kahlert, M.: Plasmochin in Autochthonous Malaria in Tropical Regions, *Philippine J. Sc.* **37**:75, 1928; *Deutsche med. Wchnschr.* **55**:1635, 1929.

17. Amies, C. R.: Use of Plasmoquine in Subtertian Malaria, *Bull. Inst. M. Research, Federated Malay States*, no. 5, 1930, p. 1.

18. Kligler, I. J., and Mer, G.: Periodic Intermittent Treatment with Chino-plasmine as a Measure of Malaria Control in a Hyperendemic Area, *Riv. di malariol.* **10**:425, 1931; *Studies on Malaria: VII. Relapse Rate After Quinine-Plasmoquine Treatment*, *Tr. Roy. Soc. Trop. Med. & Hyg.* **25**:121, 1931.

19. Manifold, J. A.: Report on a Trial of Plasmoquine and Quinine in the Treatment of Benign Tertian Malaria, *J. Roy. Army M. Corps* **56**:321 and 410, 1931.

20. Schulemann, W.: Synthetic Anti-Malarial Preparations, *Proc. Roy. Soc. Med. (Sect. Trop. Dis.)* **25**:897, 1932.

21. Bass, C. C.: Treatment of Malaria, with Some Reference to Recently Promoted New Remedies, *J. A. M. A.* **95**:988 (Oct. 4) 1930.

than plasmochin alone. As a result plasmochin compound was marketed in the form of tablets which contained 0.01 Gm. of plasmochin combined with 0.125 Gm. of quinine sulphate. The usual dose of this compound is one tablet four times a day for adults, one tablet three times a day for children from 6 to 10 years old and one tablet twice a day for children under 6 years. It is best to give a 5 grain (0.3 Gm.) tablet of quinine with each tablet of plasmochin compound.

Plasmochin compound gave more satisfactory results than plasmochin alone, but the work of Sinton and his associates,¹⁵ as well as that of others, showed that still better results could be obtained with more quinine than the compound contained. After extensive studies Sinton and his associates^{15c} concluded, among other things, that plasmochin therapy requires constant supervision and control and that quinine and plasmochin in combination are better than either drug alone in producing permanent cures in chronic benign tertian malaria. They advised that not less than 1.25 Gm. of quinine be given daily, with not more than 0.04 Gm., "perhaps 0.03" Gm., of plasmochin. They recommended that no plasmochin be given to persons suffering from diseases of the kidneys, liver or circulatory system. They also believed that a prolonged course of small doses of plasmochin is better than a shorter course of larger and interrupted doses.

Manifold,¹⁹ in India, after an adequate experiment, concluded that plasmochin and quinine combined could be given safely to all classes of British soldiers and to nearly all Indians. He observed few toxic results. He concluded that the treatment was "most efficacious in preventing relapses and a great advance on the ordinary quinine treatment." He used 0.04 Gm. of plasmochin and 1.25 Gm. of quinine daily in divided doses.

The present tendency is to give plasmochin with quinine salts in the following doses: for adults, one tablet three or four times daily, preferably after meals; for children between the ages of 1 and 5 years, half a tablet once or twice a day and for those between the ages of 6 and 10 years, half a tablet three or four times a day. As a rule, the fever will subside by the second or third day, and the parasites will disappear by the sixth or seventh day. Gametocytes are inactivated or destroyed almost at once. Treatment should be continued for two or three weeks.

Some observers, for example, Fischer and Weise²² and Napier and Das Gupta,²³ recorded a provocative action of small doses of plasmochin.

22. Fischer, O., and Weise, W.: Ueber Wirkungen und Nebenwirkungen des Plasmochins bei der Behandlung der menschlichen Malaria, *Deutsche med. Wchnschr.* 58:1380 and 1421, 1927.

23. Napier, L. E., and Das Gupta, B. M.: Atebrin: A Synthetic Drug for the Treatment of Malaria, *Indian M. Gaz.* 67:181, 1932.

The latter authors noticed this stimulating effect in an untreated patient who entered the hospital on the twelfth day of the month with a few trophozoites and crescents in the peripheral blood but with no fever. Daily examinations until the twenty-eighth revealed very few trophozoites on the twenty-second and only crescents in small numbers on the other days. On the twenty-fifth, twenty-sixth and twenty-seventh, two doses of 0.01 Gm. of plasmochin were given daily, and on the twenty-eighth there was a slight rise of temperature accompanying the reappearance of asexual forms of the parasite in blood smears. Similar results were observed by Napier, Butcher and Das Gupta.²⁴

In human as in avian malaria, plasmodia react differently to quinine and to plasmochin, according to the stage of development. They also differ in their response according to their species; in fact, even different strains or races of the same species show marked differences in their susceptibility to these drugs. Schulemann,²⁰ for example, stated that quinine is most potent against benign tertian malaria, less so against quartan and least so against estivo-autumnal malaria in the acute attacks, i.e., against newly formed schizonts. Yet quinine is less effective in preventing relapses of benign tertian malaria than in preventing those of the estivo-autumnal type. It does not act effectively on the gametocytes of estivo-autumnal malaria, but plasmochin is of value against them. Plasmochin acts on both the schizonts and gametocytes of tertian and quartan malaria, although data on this point are not complete. But plasmochin is less effective against the schizonts of estivo-autumnal malaria. Unlike quinine, plasmochin is more potent in preventing relapses of benign tertian malaria than of the estivo-autumnal form. In fact, the usual 50 per cent rate of relapse in groups of laborers with benign tertian malaria after treatment with quinine is reduced to only 2 or 3 per cent when plasmochin is added to the quinine.

As was stated in the discussion of laboratory experiments, plasmochin is more suitable than quinine for the treatment of malaria in pregnancy, because it has less effect on the uterine muscles when given in the usual therapeutic doses. Nutter,²⁵ for example, specifically mentioned treating four pregnant women with plasmochin compound, without ill effects. Similar reports have been published by Mühlens and Fischer^{26a} and by Manson-Bahr.^{14c}

24. Napier, L. E.; Butcher, D., and Das Gupta, C. R.: Field Experiments with Atebrin and Plasmochin, *Indian M. Gaz.* **67**:186, 1932.

25. Nutter, R. B.: Plasmochin, Annual Rep., M. Dept., United Fruit Company, 1926, vol. 15, p. 77.

26. Mühlens, P., and Fischer, O.: (a) Die Behandlung der natürlichen menschlichen Malaria mit Plasmochin, *Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg.* **31**:7, 1927; (b) Ueber Malariabehandlung mit Atebrin, *Arch. f. Schiffs- u. Tropen-Hyg.* **36**:196, 1932.

The successful use of plasmochin in the treatment of blackwater fever has been reported by Mühlens and Fischer, Memmi and Schulemann,²⁷ Cooke and Willoughby²⁸ and others. But some investigators, for example, Brosius,²⁹ stated that plasmochin does not prevent the development of blackwater fever.

As to the effect of plasmochin on the spleen, Miller³⁰ and Manson-Bahr,^{14a} among others, reported rapid reduction in the size of this organ following treatment with plasmochin; Miller stated that the decrease in size was much more rapid with plasmochin than with quinine.

2. *Atabrine*.—Information concerning atabrine is scanty, and the use of the drug must be considered as still in the experimental stage. Early publications seem to show that this drug has a destructive effect on the schizonts of all forms of malaria and on the gametocytes of tertian and quartan malaria but not on the crescents of estivo-autumnal infections. The dose provisionally recommended for adults is one tablet, i.e., 0.1 Gm., three times daily for a week. It is advisable, at least in cases of estivo-autumnal malaria to add to this treatment daily doses of 0.03 Gm. of plasmochin.

Among the published reports of the clinical use of atabrine should be mentioned those of Kikuth, Sioli and Peter,¹⁰ Napier and Das Gupta,²³ Napier, Butcher and Das Gupta,²⁴ Das Gupta,³¹ Mühlens and Fischer,^{26b} James and his associates,³² Thonnard-Neumann,³³ Drenowski,³⁴ Green³⁵ and Hoops.³⁶ Napier and Das Gupta, on the basis of

27. Memmi, G., and Schulemann, W.: Plasmochin, Synthetic Derivative of Quinoline, *Beihefte z. Arch. f. Schiffs- u. Tropen-Hyg.* **31**:59, 1927; *Riv. di malariol.* **6**:40, 1927.

28. Cooke, W. E., and Willoughby, H.: Note on Use of Intravenous Sodium Bicarbonate Solution in the Treatment of Blackwater Fever, *Lancet* **1**:334, 1929.

29. Brosius, O. T.: Plasmochin in Malaria, Rep. M. Dept., United Fruit Company, 1927, vol. 16, p. 26.

30. Miller, R. L.: Plasmochin in the Treatment of Malaria, *J. M. A. Georgia* **19**:363, 1930.

31. Das Gupta, B. M.: A Case of Blackwater Fever Treated with Atebrin, *Indian M. Gaz.* **67**:330, 1932.

32. James, S. P.; Nicol, W. D., and Shute, P. G.: A Study of Induced Malignant Tertian Malaria, *Proc. Roy. Soc. Med. (Sect. Trop. Dis.)* **25**:1153, 1932.

33. Thonnard-Neumann, E.: Ueber Behandlung der natürlichen Malaria mit Atebrin in Columbien, *Arch. f. Schiffs- u. Tropen-Hyg.* **36**:357, 1932.

34. Drenowski, A. K.: Therapeutische Versuche an Malariakranken mit Atebrin und Plasmochin, *Arch. f. Schiffs- u. Tropen-Hyg.* **36**:373, 1932.

35. Green, R.: Report on 50 Cases of Malaria Treated with Atebrin, a New Synthetic Drug, *Lancet* **1**:826, 1932.

36. Hoops, A. L.: The Treatment of Malaria with Atebrin in Estate Practice, *Tr. Roy. Soc. Trop. Med. & Hyg.* **26**:289, 1932.

eleven cases, concluded that atabrine in doses of 0.1 Gm. taken three times daily for four days controls fever in each of the three common forms of malaria, brings about a disappearance of asexual forms of the parasite from the peripheral blood and is neither toxic nor unpleasant to take. But they reported that atabrine did not destroy or prevent the formation of crescents of *Plasmodium falciparum*. They were not certain whether they had obtained complete cures or whether atabrine was more or less efficacious than quinine, but they believed that the results of the early experiments were encouraging. Napier, Butcher and Das Gupta, after treating a series of forty-eight patients under field conditions, concluded that atabrine in the doses used by Napier and Das Gupta exhibited "a considerable degree of efficacy," was safe and non-toxic and was suitable for use under field conditions. Hoops reported that atabrine administered under supervision is better than quinine for the treatment of malaria in estate practice. Treatment with the former drug is short, simple and less costly, and fewer relapses follow its use.

Das Gupta reported a case in which blackwater fever was successfully treated with atabrine. He used 0.1 Gm. twice a day for five days. In this case quinine had not been successful in controlling the disease; in fact, Das Gupta suggested that the hemoglobinuria was precipitated by quinine.

James and his associates³² found atabrine useful in cases of infection with strains of *Plasmodium falciparum*, against which quinine had proved to be so ineffective that permanent cure by means of it could not be brought about. In other cases, in which different geographic strains of *Plasmodium falciparum* were involved, atabrine was found to be no better than quinine. In other words, as James and his associates pointed out, there are differing strains of *Plasmodium falciparum*. There are "geographic races" not morphologically different but having distinctive properties as regards clinical virulence, immunologic reactions and other biologic phenomena, including their reaction to drugs.

In this connection, it should be noted that it is not the ingested dose but the amount of the drug circulating in the blood stream and the length of time it remains there that should be considered in all comparisons of potency. The researches of Vedder and Masen,³⁷ St. John³⁸ and others in the analyses of quinine in the blood are important. No similar work has been reported with plasmochin and so little with quinine that most explanations of variations in response to malaria therapy must be considered as tentative.

37. Vedder, E. B., and Masen, J. M.: The Determination of Quinine in the Blood as a Guide to the Treatment of Malaria, *Am. J. Trop. Med.* **11**:217, 1931.

38. St. John, J. H.: Quinine Analysis of the Blood with Reference to the Treatment of Malaria, *Am. J. Trop. Med.* **12**:101, 1932.

The research department of the Winthrop Chemical Company,³⁹ on the basis of reports concerning some seven hundred patients with malaria in different parts of the world who were treated with atabrine, has issued a statement summarizing the results. These seem to be consistent in showing that atabrine affects all forms of the three common species of plasmodia found in malaria, with the important exception of the gametocytes of the estivo-autumnal form. A further exception must be made in the case of all sporozoites. No information concerning the effect of atabrine on the latter is available. There is some evidence that atabrine actually tends to increase the number of crescents, but when plasmochin is added to the treatment, crescents are destroyed. It is not stated in the report whether quinine should be given with atabrine and plasmochin given in combination or with plain atabrine. The report stated further that splenomegaly is reduced by atabrine and that patients with blackwater fever have been successfully treated with this drug.

Mühlens⁴⁰ recently suggested the following method of treating malaria: 1. Estivo-Autumnal Malaria: For three days give one tablet each of atabrine (0.1 Gm.) and plasmochin simplex (0.01 Gm.) three times a day. Then for four days give only the tablet of atabrine (0.1 Gm.) three times a day. 2. Tertian and Quartan Malaria: Give simply one tablet of atabrine (0.1 Gm.) three times a day for from five to seven days. He stated that in his experience relapses did not occur after this treatment.

Among the ill effects of atabrine which are occasionally observed is a yellowish discoloration of the skin, due, it is said, to temporary deposition of the drug. This discoloration disappears within a period ranging from a few days to four weeks, without deleterious effect. Under treatment with atabrine and plasmochin given in combination there have been instances of abdominal pain similar to that which is sometimes observed following treatment with plasmochin.

SUMMARY

1. The origin and general nature of plasmochin, plasmochin compound, plasmochin with quinine salts and atabrine are briefly discussed, and a description is given of the forms in which each is available.

2. A number of laboratory experiments with these drugs, carried out by various observers, including myself, are discussed. From these it may be concluded that although the various avian malarias react differently to plasmochin and plasmochin with quinine salts, they are all

39. Winthrop Chemical Company, New York. Laboratory and clinical data concerning atabrine, prepared and mimeographed by the Department of Research Medicine, 1932.

40. Mühlens, P.: A lecture given on March 21, 1933, at the School of Hygiene and Public Health, University of the Philippines, Manila.

affected by it and by atabrine. Plasmochin combined with quinine is more effective than either drug used alone. Plasmochin in vitro is toxic to schizonts, more so to some species than to others. Plasmochin in doses exceeding the therapeutic limit causes uterine contractions in cats and guinea-pigs and cardiac arrhythmia in cats and rabbits. The effect on the uterus is not seen after therapeutic doses, and the disturbance of cardiac rhythm is not present when quinine is administered with the plasmochin.

3. The practical therapeutic usefulness of plasmochin, plasmochin compound, plasmochin with quinine salts and atabrine is considered, and reports of research workers in various parts of the world are given. It is concluded that plasmochin is best administered as plasmochin with quinine salts. Not more than 0.04 Gm. of plasmochin per day should be given to adults, and the administration of at least 1.25 Gm. of quinine in addition to or combined with the plasmochin is advisable. Larger doses of plasmochin produce toxic symptoms. Treatment should, as a rule, extend over two or three weeks.

4. It is concluded that plasmochin is not a substitute for quinine but an adjuvant to it. Quinine and plasmochin given in combination represent a distinct advance in malaria therapy. It is too early to draw definite conclusions concerning the merits of atabrine.

5. Not all cases of malaria are alike, and treatment should be given according to the characteristics of the plasmodium involved. Some patients react better to quinine; others, to plasmochin; others, perhaps, to atabrine. Plasmodia differ in their susceptibility to drugs according to stage of development, strain and species. Intelligent therapy will make use of these differences.

Book Reviews

The Technic of Local Anesthesia. By Arthur E. Hertzler, A.M., M.D., Ph.D., LL.D., Professor of Surgery, University of Kansas; Surgeon to the Halstead Hospital, Kansas. Fifth edition. Price, \$5. Pp. 292, with 148 illustrations. St. Louis: C. V. Mosby Company, 1933.

In 1912 the Surgery Publishing Company of New York put out an unassuming small book called "Surgical Operations with Local Anesthesia," by Arthur E. Hertzler. The topic was something of a novelty, but the book was clearly written and well illustrated, winning at once a high degree of popularity. A second edition was necessary in 1916, which was considerably larger and better illustrated than the first. This was also enthusiastically received by students, surgeons and reviewers. In 1925 the C. V. Mosby Company published the third edition of the book under its present name. *The Journal of the American Medical Association* (84:1943 [June 20] 1925) devoted half a column to it, ending the review, after certain mild rebukes, in much the fashion of earlier reviewers: "These are minor criticisms, and are not meant as a criticism of the work as a whole, which is excellent and can be highly recommended." The fourth edition appeared in 1928, and now the fifth edition is off the press.

Any medical book which is only 21 years old and popular enough to have gone through five editions in so short a time is of necessity a first-class book. The original model was obviously built on serviceable lines, and the author has been sensible enough to retain its general plan in each ensuing edition. The latest publication, therefore, is much like its predecessors and is entirely praiseworthy. The chapter on spinal anesthesia has been rewritten, and a short chapter on intravenous anesthesia has been added to bring the subject up to date. The book as a whole continues to be informative, interesting, well illustrated and worth owning.

Strophanthin Therapy: Also Comments on the Quantitative Administration of Digitalis According to Pharmacologic Principles. By Prof. Dr. A. Fraenkel, in collaboration with Dr. R. Thauer. Pp. 144. Berlin: Julius Springer, 1933.

This monograph is amazingly complete in detail and is presented in a meticulously orderly and systematic manner. While the reader is at times burdened by detail, the work as a whole is very interesting.

The authors introduce the subject in a fascinating manner by relating the history of strophanthus. It was first introduced and grown in western Europe in 1800 by the French botanist, Descandolle. The interesting episode of Kirk's accidental discovery of its cardiac action while on Livingstone's expedition in Zambesia is told. The botanic facts regarding the plant are described in considerable detail, as are also the pharmacology and chemistry of strophanthin.

Every conceivable phase of the subject is considered, with emphasis on the indications, contraindications, methods of administration and results. After reading this monograph, one is led to wonder whether American physicians have accorded strophanthin proper recognition as a valuable cardiac drug.

Les grandes hémorragies gastro-duodénales. Étude Médico-Chirurgicale. By Louis Tixier and Charles Clavel. Price, 45 francs. Pp. 240. Paris: Masson & Cie, 1933.

This work is in accord with the French custom of treating a circumscribed aspect of medicine in monographic form. All types of gastroduodenal bleeding are discussed with the greatest thoroughness from every possible standpoint—clinical, anatomic, therapeutic and surgical. There are detailed case reports and

many illustrations. While a great amount of valuable material is assembled, one may make the criticism that very little is brought out which is not, or at least should be, common knowledge even among junior medical students, and a good many points are labored at undue length. The book contains a mine of material, however, and seems to give the last word on the subject. A good deal of discussion is devoted to indications for surgical intervention in cases of bleeding from the stomach. The authors point out that erosions of large arteries rarely heal spontaneously, and that the bleeding point should be ligated. They also admit the difficulty of making an exact diagnosis of this sort of accident and the further difficulty, often, of discovering the bleeding artery after the stomach has been opened. On the whole the reviewer would take a somewhat more conservative position than the authors; he believes that only occasionally is it advisable to operate during the course of gastric bleeding, as death, after all, rarely occurs purely from this cause.

Food, Nutrition and Health. By E. V. McCollum, Ph.D., Sc.D., and J. Ernestine Becker, M.A. Price, \$1.50. Pp. 146. Published by the authors, Baltimore.

This book, now appearing in its third edition, is a most helpful guide in a day of general interest in foods and diets. The authors are head and associate, respectively, of the Department of Biochemistry of the School of Hygiene and Public Health of Johns Hopkins University. The book is, therefore, thoroughly authoritative. It contains a nontechnical account of the discoveries of nutrition and is of special service to both layman and physician as a corrective for the mass of misleading information being disseminated today by commercial interests and by the faddist.

The authors explain in simple language the essentials of a completely satisfactory diet, as revealed by the newer science of nutrition. The effects of deprivation of individual nutrients are explained; the kinds of malnutrition and their extent are described, and a system of diet is recommended which is sound not only from the physiologic but also from the economic standpoint.

The book is highly recommended for use in the medical school, in the office of the medical practitioner and in the household where interest has been aroused in matters of dieting and nutrition.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Edited by Prof. Dr. Bruno Kisch, Köln. Price, 15 marks. Pp. 276, with 97 illustrations and 35 charts. Dresden: Theodor Steinkopf, 1933.

This book, as the title indicates, consists of the papers presented at the sixth annual meeting of the Society. In addition to the president's address, there are twenty-eight papers together with the discussions. The papers cover all branches of the study of the circulation. Blood pressure, heart failure, the carotid sinus, electrocardiography, the vasomotor nerves and the parasympathetic and sympathetic systems are accorded a share of attention. The papers are profusely supplied with diagrams, charts and electrocardiograms.

The work is for the most part the result of experimentation on animals. There are a fair number of papers dealing with clinical observations of an experimental nature and a few purely clinical reports.

The work is well done but very highly specialized. For the research worker in this field or for the clinician who limits himself entirely to diseases of the circulation this book will prove extremely interesting and helpful. Apart from these groups its place is in the reference library, and it should be found in all good ones.

Chronic Indigestion. By Thomas C. Hunt. Price, \$4.25. Pp. 341. Baltimore: William Wood & Company, 1933.

The material in this monograph is concisely and ably presented, and it will doubtless prove of value to students and practitioners alike. The author strives to give a practical outline of present-day views on chronic indigestion and related syndromes, based on personal experiences.

The first ten chapters are devoted to a discussion of the commoner organic and functional derangements of the gastro-intestinal tract. Accompanying each chapter are plates illustrating characteristic lesions as shown by roentgen examination. The routine laboratory procedures employed in this field are described, and a section is devoted to the taking of case histories, physical examination and special investigations.

A few prescriptions suitable for the treatment of "chronic indigestion" are included, the drugs employed being those in general use and of recognized value. A bibliography of about 168 references is included.

Surgery of the Stomach and Duodenum. By J. Shelton Horsley. Price, \$7.50. Pp. 260. St. Louis: C. V. Mosby Company, 1933.

In this volume Dr. Horsley says about all there is to say on gastric surgery. The stage is set by brief chapters on embryology, anatomy and the physiology of the stomach, which are followed by detailed descriptions, well illustrated, of the various procedures. The reviewer is not competent to discuss the finer points of surgical technic. He does disagree, however, with some of the physiologic considerations which are supposed to furnish a rational basis for certain procedures. In his experience, for example, it is difficult to predict the results obtained by surgical intervention in cases of peptic ulcer. Sometimes the patient is helped; occasionally he is made worse. The effects are difficult to correlate with the mechanical changes which have been produced. The book is nicely gotten up, but the price is considered to be excessive.

Die Luft- und Fettembolie. By Siegfried Hoffheinz, M.D. Paper. Price, 29 marks. Pp. 259, with 50 illustrations. Stuttgart: Ferdinand Enke, 1933.

The author of this monograph gives an excellent account of air embolism and fat embolism. Both subjects are discussed systematically, in detail, and in much the same manner: historically, from the point of view of their pathology and pathologic physiology, and finally as clinical entities. A comprehensive bibliography completes the volume.

Such a book, dealing with two relatively uncommon surgical problems, is unlikely to acquire much popularity among general readers. As a reference book, however, it is to be recommended.

News and Notes

SURVEY OF INCIDENCE OF CRETINISM

A survey of the incidence of cretinism in the United States is proposed by Dr. Arnold Jackson (16 S. Henry Street, Madison, Wis.), who respectfully requests that physicians who have had such cases send to him the following information regarding them, together with photographs if possible: name and address of the patients, in order to obviate duplication; nativity; brief physical characteristics; brief clinical history; presence or absence of goiter; mental status, and the results of medication.

RELATIONSHIP BETWEEN ANATOMIC CHANGES IN KNEE JOINT WITH ADVANCING AGE AND DEGENERATIVE ARTHRITIS

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The acquirement of knowledge concerning arthritis has been delayed by a lack of detailed information regarding the changes which may be encountered with advancing age. Such information is highly desirable in order to assist in defining the limits of normal for a given age period. It is of further importance from the point of view of the ultimate changes that may occur in a joint which has been the site of an injury resulting from invasion by infective agents, and, finally, it provides knowledge regarding the early stages of disorders of the joints. For these reasons we have made a systematic study of 100 knee joints removed at consecutive necropsies, and in this article we detail the gross anatomic findings and discuss their significance.

MATERIAL AND METHODS

One hundred knee joints were removed from 77 cadavers. The cases were not selected on the basis of previous clinical diagnosis or the presence of symptoms in the joints. The only cases excluded from the group were those in which there was definite infection of the joints with various organisms, as determined by bacteriologic examination of the fluid found in the joints at necropsy. A study of these joints will be presented separately. Whenever possible, the whole knee joint was removed together with its capsule and a portion of the femur and tibia. When this was not feasible, the joint was opened by cutting across the inferior patellar ligament and reflecting the patella. The articular surfaces of the *patella*, *femur* and *tibia* were then removed in such a way that the surfaces could be reconstructed and studied. The gross changes were noted, and material was taken for histologic section.

In this paper the term degenerative arthritis is used synonymously with hypertrophic arthritis and osteo-arthritis.

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ANATOMIC CONSIDERATIONS

It is not our purpose to comment in detail on the anatomy of the knee joint. It is necessary to know some of the salient facts before one can clearly understand the changes which were found. The relevant facts are recalled herewith.

The articulations of the knee joint are divided into the following groups: (1) the articulation of the patella with the femur, and (2) the articulations of the two condyles of the femur with the corresponding meniscus and condyle of the tibia.

The articulation of the patella with the femur is partly a gliding one, but as the articular surfaces are not mutually adapted to each other, the movement is not a simple gliding one. This fact will become obvious when the various movements of the knee joint are analyzed in detail.

For the purpose of describing the movements of the patella and its articular surface, it may be divided roughly into seven facets: the upper, middle and lower horizontal pairs and a median perpendicular facet.

The surface of the femur which articulates with the patella is named the patellar or anterior surface. It presents a median groove which extends downward to the intercondyloid fossa and two convexities, the lateral one of which is broader and more prominent and extends farther upward than the medial. In the extended position of the leg, when the quadriceps femoris is relaxed, the patella lies loosely on the front of the lower end of the femur. When the knee is forcibly flexed the median perpendicular facet is in contact with the semilunar surface of the lateral part of the medial condyle of the femur; this semilunar surface is a backward prolongation of the medial part of the patellar surface of the femur. As the leg is carried from the flexed to the extended position, first the upper, then the middle and finally the lowest pair of horizontal facets is successively brought into contact with the patellar surface of the femur. In the process of walking, in which the leg is alternately extended and semiflexed, the part of the patella which is brought into contact with the femur is the median pair of horizontal facets. The importance of this will be stressed presently.

The lower and posterior parts of the articular surface of the femur constitute the tibial surfaces for articulation with the corresponding condyles of the tibia and menisci. These surfaces are separated from one another by the intercondyloid fossa and from the patellar surface by faint grooves which extend obliquely across the two condyles. The lateral groove is better marked; it runs lateralward to form a triangular depression.

The articular surface of the tibia consists of two facets, the central portions of which articulate with the condyles of the femur, while their peripheral portions support the menisci of the knee joint which here

intervene between the two bones. Between the two facets is the intercondyloid eminence, surmounted on either side by a prominent tubercle, onto the sides of which the articular facets are prolonged. The lateral condyle is usually somewhat smaller than the medial and is nearly circular.

In the position of extension, when the subject is standing erect, the weight of the trunk is transmitted from the head of the femur in a vertical line which passes through the external condyle of the femur and tibia.

When full extension of the leg is reached and maintained the lateral part of the groove of the lateral condyle of the femur is pressed against the anterior part of the corresponding meniscus, while the medial part of the groove rests on the articular margin in front of the lateral process of the tibial intercondyloid eminence. Into the groove on the medial condyle is fitted the anterior part of the medial meniscus, while the anterior crucial ligament and the articular margin in front of the medial process of the intercondyloid eminence are received into the forepart of the intercondyloid fossa of the femur.

In full flexion, the posterior parts of the femoral condyles rest on the corresponding parts of the meniscotibial surfaces, and the semilunar area of the median condyle articulates with the median vertical facet of the patella. As the limb moves from flexion to extension the posterior two thirds of the tibial articular surfaces of the two femoral condyles gradually shift forward and the patella moves upward in the manner previously described.

In walking, greater weight is placed on the lateral condyle of the tibia than on the median, and the inferior surface of the femoral condyles articulates with the corresponding articular surfaces of the tibial condyles. With these facts borne in mind, the results of our investigation are detailed.

Sex and Age.—Of the 100 joints, 67 were obtained from males and 33 from females. From tables 1, 2 and 3, it is seen that the changes observed were as common in women as in men. No qualitative difference in the type of anatomic alterations in the joints was observed. For these reasons the gross changes in the two sexes are considered together.

The age distribution of the patients whose joints were studied is given in figure 1. In figure 2 the total percentage of joints showing changes at various age periods is shown, and it is obvious that the anatomic deviations from normal increase with advancing age.

Occupation.—As degenerative arthritis is sometimes explained on the basis of a person's occupation or at least is aggravated by certain occupations that require the excessive use of the joints, an analysis was made of the patients' occupations. They are summarized in table 4.

TABLE 1.—*Site of Observed Anatomic Changes in the Knee Joints in Various Decades of Life (Males)*

Age, Years	Number of Joints	Patella	Femur			Tibia	
			Interpatellar Groove	Median Condyle	Lateral Condyle	Median Condyle	Lateral Condyle
0-9.....	2	0	0	0	0	0	0
10-19.....	0	0	0	0	0	0	0
20-29.....	0	0	0	0	0	0	0
30-39.....	4	1	1	0	0	2	2
40-49.....	8	4	3	1	0	2	4
50-59.....	14	13	9	7	4	9	9
60-69.....	17	16	13	7	3	10	11
70-79.....	16	15	15	11	11	10	12
80+.....	6	5	3	2	2	4	4
Total.....	67	54	44	28	20	37	42

TABLE 2.—*Site of Observed Anatomic Changes in the Knee Joints in Various Decades of Life (Females)*

Age, Years	Number of Joints	Patella	Femur			Tibia	
			Interpatellar Groove	Median Condyle	Lateral Condyle	Median Condyle	Lateral Condyle
0-9.....	1	0	0	0	0	0	0
10-19.....	2	0	0	0	0	0	0
20-29.....	1	0	0	0	0	0	0
30-39.....	2	1	1	0	0	1	1
40-49.....	1	0	0	0	1	0	0
50-59.....	6	5	4	4	4	4	6
60-69.....	11	12	10	6	6	7	8
70-79.....	8	4	3	2	2	2	2
80+.....	6	5	3	3	3	4	5
Total.....	33	27	21	15	16	18	22

TABLE 3.—*Total Changes in Both Sexes, Showing Site of Anatomic Alterations*

Age, Years	Number of Cases	Number of Joints	Patella	Femur			Tibia	
				Median Condyle	Lateral Condyle	Interpatellar Groove	Median Condyle	Lateral Condyle
0-9	3	3	0	0	0	0	0	0
10-19	2	2	0	0	0	0	0	0
20-29	1	1	0	0	0	0	0	0
30-39	5	6	2	0	0	2	3	3
40-49	7	9	4	1	1	3	2	4
50-59	14	20	18	11	8	13	13	15
60-69	23	28	28	13	9	23	17	19
70-79	15	19	19	13	13	18	12	14
80+	7	12	10	5	5	6	8	9
Total	77	100	81	43	36	65	55	64

TABLE 4.—*Occupations of the Patients*

Laborers.....	30
Housewives.....	21
Artisans.....	17
Cooks and waiters.....	4
Workers in offices.....	4
Professional worker.....	1

In a further analysis of the extent of anatomic change and occupation we were unable to determine any relationship between the extent of the damage and the occupation, but data concerning the actual details of the patients' life-long daily careers were not available.

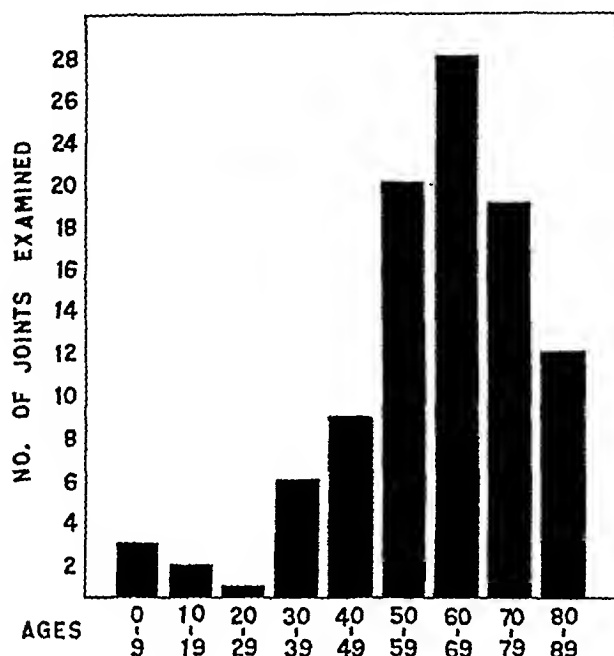


Fig. 1.—Age distribution of the 77 patients whose knee joints were examined.

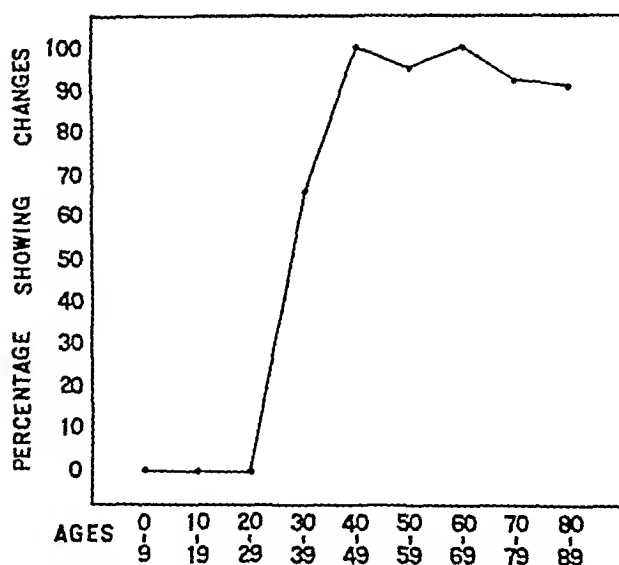


Fig. 2.—The percentage of cases showing anatomic changes in the knee joints at different age periods.

Cause of Death.—The diseases from which the patients died are listed in table 5. From this table it is seen that no one disease or group of diseases could be held responsible for the changes observed.

Relationship Between Anatomic Lesions and Symptoms Referable to the Joints.—There were no symptoms recorded in the clinical his-

tories of 66 patients, and pain and stiffness were present in only 11 of the 77 patients. When symptoms referable to the joints are present in a patient with anatomic changes in the joints such as we have observed, it is necessary to look for other factors in order to explain the symptoms. From our observations it is manifest that pathologic changes in the joints were present with equal frequency in both sexes, that they increased in frequency with advancing age and that neither the cause of death nor the occupation of the patients was of significance in accounting for the condition of the joints.

Changes in the Patella.—The articular surface of the patella showed distinctive alterations in 81 of the joints examined. The sites of the changes are recorded in table 6. In most cases the median surface

TABLE 5.—*Diseases Responsible for Death*

Lobar pneumonia and bronchopneumonia.....	20
Arteriosclerotic heart disease.....	15
Cancer (miscellaneous)	10
Cerebral hemorrhage	6
Tuberculosis	8
Peritonitis (generalized)	3
Pyelonephritis	5
Rheumatic heart disease.....	4
Syphilitic aortitis with aneurysm or aortic insufficiency.....	2
Pernicious anemia	1
Aplastic anemia	1
Osteogenic sarcoma	1
Bacterial endocarditis	1
Total.....	77

TABLE 6.—*Position of Changes in the Patella*

	Median Surface	Lateral Surface
Superior horizontal facets.....	14	17
Median horizontal facets.....	75	61
Inferior horizontal facets.....	22	19

showed alterations more often than the lateral surface, and the median horizontal facets were involved more often than the other two pairs. This is significant because this is the part of the patella which comes in contact with the patellar surface of the femur most frequently in such movements as walking. The inferior pair were changed more often than the superior, and again this pair of facets comes in contact with the femur more often than the superior pair.

The character and degree of the erosions varied tremendously in different cases. Figure 3 illustrates the kind of alterations observed. It is seen that there may be simple fibrillation of the cartilage, with irregularity of the surface or loss of varying amounts of cartilaginous substance so that in some cases the underlying bone is exposed. In the places where the bone was exposed it was usually very dense and, in some cases, shiny, giving an appearance of a highly polished surface, the so-called eburnated bone.



Fig. 3.—Photographs of the articular surface of the patella, showing the type of anatomic alterations observed. Various degrees of changes are present. In some cases there is only fibrillation of the cartilage; in others the underlying bone is exposed.



Fig. 4.—Photographs of the patellar groove of the femur, illustrating the type of lesion observed. The lesion is progressively more extensive in the specimens shown.

Femur.—For purposes of discussion we have divided the articular surfaces of the femur into the patellar groove, the anterior and posterior articular surfaces of the condyles and the median surface of the median condyle.

Patellar (Intercondyloid) Groove: This area of the femur was altered in 65 cases. In every case the erosion was situated at the point where the patella comes in contact with the femur. In most instances the eroded area was in the center of the groove; in others, it was at the right or left, depending on the size, shape and position of the patella when in contact with the femur. Figure 4 illustrates the site and type

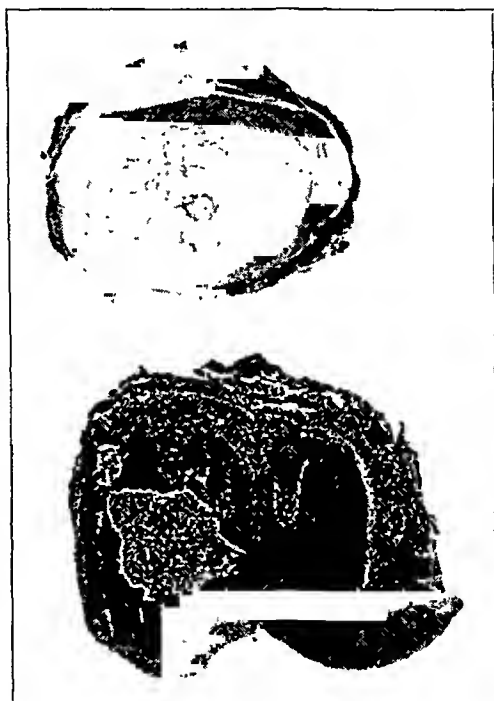


Fig. 5.—Photograph of the articular surface of the patella and the patellar groove of the femur, showing the erosions on the articulating surfaces.

of the erosions which were seen. In every case in which changes were observed in the interpatellar groove there was an irregular or eroded area on the patella at the point where it came in contact with the femur. This is illustrated in figure 5. The recognition of this fact is highly important in interpreting the findings.

Anterior Articular Surface of Femoral Condyles: It is to be recalled that the medial and lateral anterior articular surfaces of the femoral condyles come in contact with the tibial condyles and the corresponding menisci. The median condyle showed erosions in 46 joints and the lateral condyle in 36. These areas were most conspicuous at the point where the condyles were in contact with the central portion

of the tibia which was uncovered by the lateral or median meniscus. An example of these erosions is shown in figure 6.

Aside from the lesions on the anterior articular surface, erosions were observed on the median surface of the median condyle in 9 cases. They are illustrated in figure 7 and require special comment. It has already been pointed out that when the leg is in full extension the medial process of the intercondyloid eminence of the tibia and the anterior cruciate ligament are received into the forepart of the intercondyloid fossa of the femur. When a large number of these joints are examined, it becomes apparent that in some cases this eminence is high and promi-

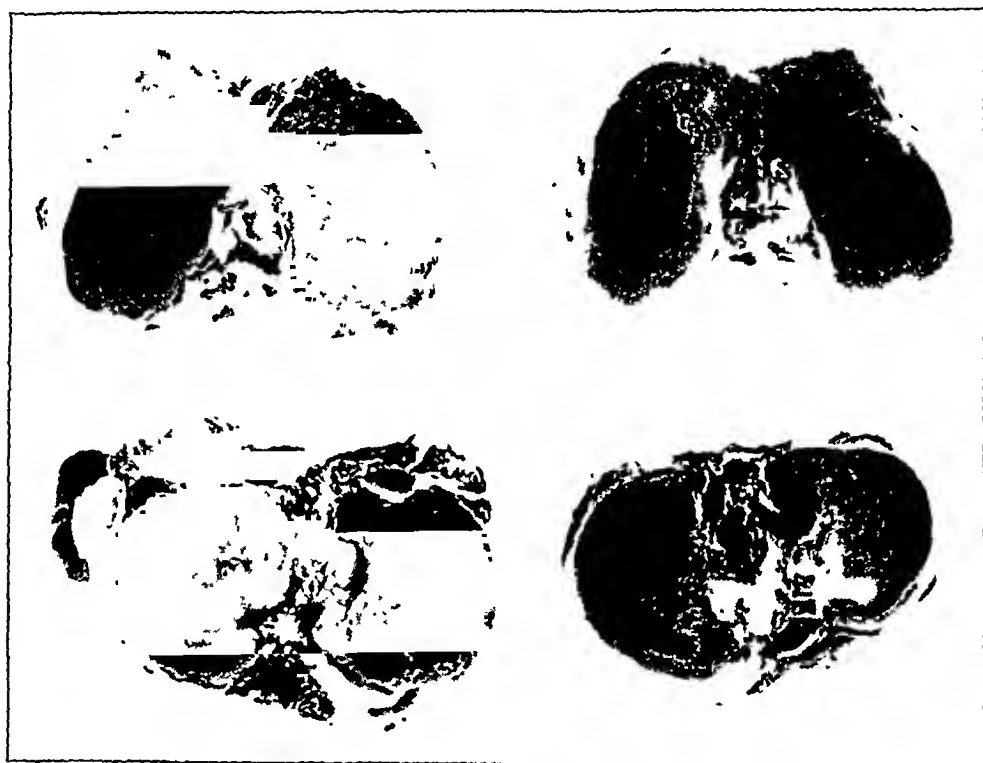


Fig. 6.—Photograph of the inferior articular surfaces of the femur and the corresponding articular surfaces of the tibia, showing the type and position of the irregularities and erosions.

nent and is in direct contact with the lateral surface of the median condyle, especially during flexion and extension. In every case in which we observed an erosion of the femur in this area the intercondyloid eminence was prominent and came in close contact with the femur, especially during the movements of semiflexion and extension. We are of the opinion that this observation is of importance in explaining the development of erosions in the area mentioned.

The posterior parts of the femoral condyles, which rest on the corresponding tibial surfaces during full flexion, showed erosions seven times on the medial condyles and five times on the lateral condyles. As

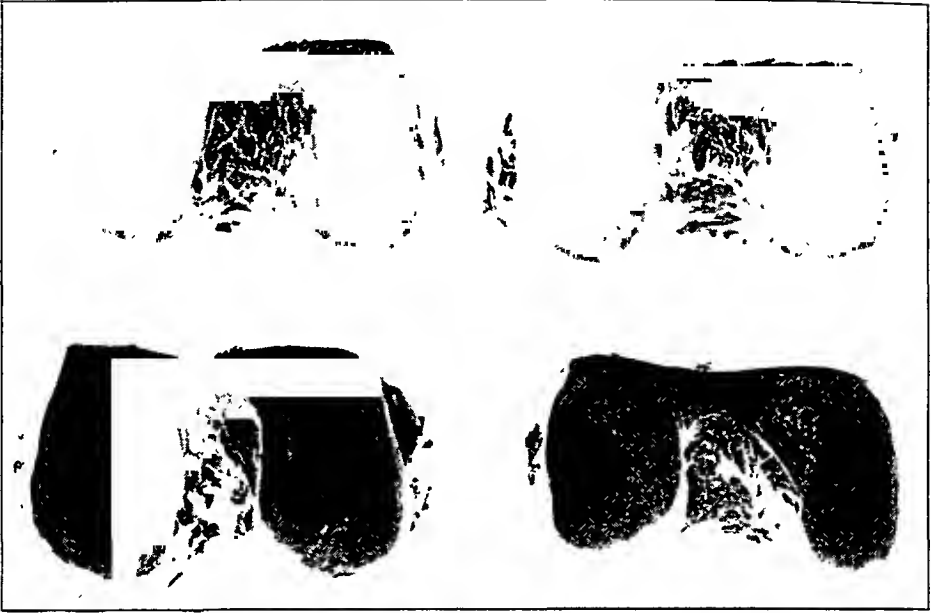


Fig. 7.—Photograph of the femoral condyles, showing erosions on the median aspect of the median condyle of the femur. This is the area of the femur which comes in contact with the intercondyloid tubercle of the median condyle of the tibia.

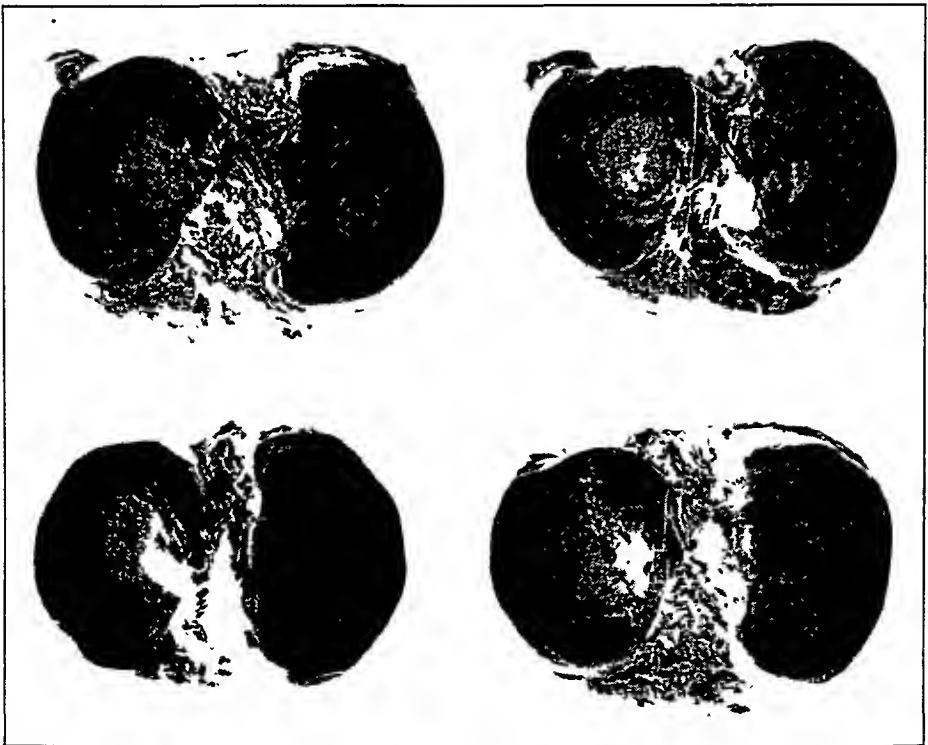


Fig. 8.—Photograph of the tibial condyles, showing areas of erosion. Note the erosions in the central part of the tibial condyles or the part of the surface which is uncovered by the semilunar cartilage.

the leg is in full flexion less frequently than in the other positions, these areas are in contact with one another less often. This probably accounts for the small number of erosions in this area.

Tibia.—The central portion of the lateral condyle of the tibia showed erosions or marked thinning of the cartilage in 64 cases, and the median condyle in 55 cases. The area of the tibial condyles which was covered by the menisci never showed erosions or thinning when the menisci were normal and were everywhere intact. When they were torn or displaced in such a way that they no longer protected the periphery of the tibia, erosions were frequently observed. Figure 8 illustrates the areas of the tibia usually involved. Here again it often was observed that the area of the tibia which was involved was opposite to an erosion on the corresponding articular surface of the femur.

Synovia.—The synovial membrane was smooth and glistening in 44 cases. In the remaining cases it ordinarily showed villous projections from the surface. It was not unusual to see the synovial membrane extending over the medial edge of the patella and, in many instances, projecting into the depressions made by the erosions in the cartilage. The villous projections increased in frequency with advancing age and were most striking in the patients with the most extensive alterations in joint structure.

COMMENT

From the data presented certain facts are clear. In the first place, anatomic changes in the knee joint were observed with increasing frequency with advancing age. The articular surface of the patella showed changes most often, and these changes were most conspicuous on the median articular facets. As we have said before, this is the part of the patella which comes in contact with the femur most often during such movements as walking. The interpatellar groove of the femur, or the area over which the patella glides, was the second most frequent site of erosion; then, in order, the lateral articular surface of the tibia, the median articular surface of the tibia and the median and the lateral condyles of the femur. On careful analysis it was obvious that the areas usually affected were those subjected to the greatest movement or weight, and this was particularly true of the points at which the articular surface came in contact during movement.

Previous observations have been made on the changes in the knee joints of patients who were not considered to be suffering from arthritis. Rimann¹ found changes in the joints of 67 of 100 persons between the ages of 15 and 80 who were examined at necropsy, and Beitzke,²

1. Rimann, H.: Arb. a. d. path. Inst. zu Berlin z. Feier 1:139, 1906.

2. Beitzke, H.: Ueber die sogenannte Arthritis deformans atrophica, Ztschr. f. klin. Med. 74:215, 1912.

on examining 200 bodies, found only 35 without alterations in some of the joints. Six showed anatomic changes of ordinary arthritis deformans, and in 16 there was evidence of gout. Of the remaining 178, visible changes were seen in the joints of 143. These changes were alike in the two sexes. Between the ages of 20 and 40 years 60 per cent of the joints showed changes; between 40 and 50 years, 95 per cent, and in older persons, 100 per cent. Clark³ studied the lesions in the joints in 1,100 cases which came to autopsy in Panama; he found gross lesions in the joints in 15.6 per cent of the patients, and of these less than 1 per cent were considered to be suffering from arthritis. He emphasized syphilis, arteriosclerosis and hard work as important etiologic factors. The most recent observations are those of Heine,⁴ who described the changes in 1,994 knee joints of patients varying from 15 to 89 years of age. Here again the changes increased with advancing age and varied from 1.5 per cent in the age period from 15 to 19 years to 100 per cent in the older age groups. The patella was involved most frequently and, as in our observations, the commonest point was the central or median facets. On the femur the interpatellar groove showed erosions most often, and the tibia was altered almost as frequently as the patella, the lateral condyle being involved more often than the median. In 490 cases, or 49 per cent, the changes were equal on both sides; in 35 per cent the right side showed greater changes than the left, and in 16 per cent the left side showed more changes than the right. The lesions occurred with equal frequency in males and females. It is evident, therefore, that in spite of the fact that the number of cases which we have observed is relatively small, lesions were observed in practically the same locations and with the same frequency by other investigators. Meyer⁵ and Keyes⁶ noted changes in the knee joints of cadavers which were similar to those observed by us, and Bennett and Bauer⁷ made similar observations in patients who had no symptoms referable to the joints during life.

What has been said regarding the knee joint is true for other joints as well. According to Heine, the joints which show lesions most fre-

3. Clark, H. C.: Etiologic Factors in Gross Lesions of the Large Joints; Observations from 1,100 Consecutive Necropsies, *J. A. M. A.* **69**:2099 (Dec. 22) 1917.

4. Heine, J.: Ueber die Arthritis deformans, *Virchows Arch. f. path. Anat.* **260**:521, 1926.

5. Meyer, A. W.: Further Observations upon Use-Destruction in Joints, *J. Bone & Joint Surg.* **4**:491, 1922.

6. Keyes, E. L.: Erosions of the Articular Surfaces of the Knee Joint, *J. Bone & Joint Surg.* **15**:369, 1933.

7. Bennett, G. A., and Bauer, W.: A Systematic Study of the Degeneration of Articular Cartilage in Bovine Joints, *Am. J. Path.* **7**:399, 1931.

quently with increasing age are the knee, acromioclavicular, elbow, hip and metatarsal joints, the joints of the spine and the sternoclavicular and shoulder joints. Zöllner⁸ and Smith-Petersen⁹ have shown the same to be true in regard to the sacro-iliac joint. Sievers¹⁰ studied the 77 acromioclavicular joints and obtained similar results. Ely¹¹ observed changes in the sternoclavicular joints at necropsy, although he did not state whether the alterations increased in frequency with advancing age.

From the recorded observations and from our own, it is difficult to escape the conclusion that the changes which are commonly observed in the joints with advancing age are precisely the same as those described as being characteristic of so-called degenerative arthritis. It is necessary, therefore, to inquire into some of the factors which have been held responsible for this disorder.

Degenerative arthritis is frequently considered to develop as the result of certain occupations. One of the first investigators to emphasize this point of view was Lane.¹² Since 1886 his observations have been confirmed repeatedly. Recently Fischer¹³ and others made the interesting observation that degenerative arthritis commonly develops in the elbow and metacarpal and shoulder joints of men who work with compressed air hammers. The changes in the joints appear anywhere from three to ten years after work with these tools and Fischer was of the opinion that repeated small traumas from the constant jarring of the hammer are mainly responsible for the development of this disorder. On the other hand, Fischer was unable to demonstrate that arthritis in the knee was more common in any particular occupation. He pointed out, however, that workers who carry heavy weights and who work in a kneeling position get arthritis, but he considered that occupation alone was the cause in only a few cases. Of greater importance in accounting for the changes in the knee are static, functional

8. Zöllner, F.: Untersuchungen über die Erscheinungsformen der Arthritis deformans in den Sacro-Iliacalgelenken, *Virchows Arch. f. path. Anat.* **277**:817, 1930.

9. Smith-Petersen, M. N.: Traumatic Arthritis, *Arch. Surg.* **18**:1216 (April) 1929.

10. Sievers, R.: Arthritis deformans des Akromioklavikulargelenks: zugleich ein Beitrag zur traumatischen Entstehung der Arthritis deformans chronica, *Virchows Arch. f. path. Anat. (supp. 1)* **226**:123, 1919.

11. Ely, L. W.: A Study of the Sterno-Clavicular Joint, in Ely, L. W., and Cowan, J. F.: Bone and Joint Studies, Stanford University, Calif., Stanford University Press, 1916, p. 121.

12. Lane, W. A.: Some Points in the Physiology and Pathology of the Osseous Systems of Trunk and Shoulder Girdle, *Guy's Hosp. Rep.* **28**:321, 1886.

13. Fischer, A.: Rheumatismus als Berufskrankheit, *Acta rheumatol.* **4**:24, 1932.

or traumatic factors. Flatfeet and rachitic deformities of the hips or knees (coxa vara or genu valgum) were found to be of great importance in producing arthritis of the joints of the lower extremities. From a study of the occupation of our patients it was not possible to show any correlation between the changes in the knee joints and the type of work done by the patients, although complete details of the work are lacking. As the changes were the same in both sexes, it would appear that the alterations in the knee joints which we studied will have to be explained on some basis other than occupation. Heine was of the opinion that factors other than the type of occupation were accountable for the changes in the joints which he observed, but Pommer,¹⁴ on the other hand, has repeatedly expressed the opinion that occupation is of great importance in degenerative arthritis, and he has quoted a number of observers who support this belief.

Of more importance than occupation in explaining the changes in the knee joints is the question of mechanical factors due to trauma, static defects and incongruities of the articular surfaces. The mechanico-functional theory of the production of the degenerative arthritis has received support from the observations of many investigators. Beneke,¹⁵ as a result of his studies in spondylitis deformans, concluded that the primary change in this disorder was degeneration of the intervertebral disks and that the changes in the vertebra resulted from continuous trauma caused by the degeneration. It is known now that the intervertebral disk becomes less elastic with advancing age, as is shown by the decreasing water content of the nucleus pulposus and the narrowing of the intervertebral space. This allows the anterior part of the vertebral bodies to come in contact during movement so that lipping and the characteristic arthritic changes in the spine occur. These changes in the spine have been produced experimentally in dogs by Keyes and Compere¹⁶ by reducing the intervertebral space so that the vertebral bodies impinged on one another during movement.

To Preiser¹⁷ belongs the credit for having emphasized the great importance of static defects in producing degenerative arthritis. As a

14. Pommer, G.: Ueber die mikroskopischen Kennzeichen und die Entstehungsbedingungen der Arthritis deformans (nebst neuen Beiträgen zur Kenntnis der Knorpelknötchen), *Virchows Arch. f. path. Anat.* **263**:434, 1927.

15. Beneke, R.: Zur Lehre von der Spondylitis deformans, *Versamml. d. deutsche Naturf. u. Aerzte, Braunschweig*, 1897, p. 109.

16. Keyes, O. C., and Compere, E. L.: The Normal and Pathological Physiology of the Nucleus Pulposus of the Inter-Vertebral Disc, *J. Bone & Joint Surg.* **14**:897, 1932.

17. Preiser, Georg: Statische Gelenkerkrankungen, Stuttgart, Ferdinand Enke, 1911; Ueber die Arthritis deformans coxae; ihre Beziehungen zur Roser Nélatonschen Linie und über den Trochanter Hochstand, Hüftgesunder infolge abnormaler Pfannenstellungen, *Deutsche Ztschr. f. Chir.* **89**:591, 1907.

result of numerous clinical observations he demonstrated that static deformities cause incongruities of the articular surfaces which lead to abnormal pressure and weight in certain parts of the joint and to the subsequent changes due to the trauma caused by weight and movement. Pommer,¹⁴ on the basis of extensive microscopic studies of the joints, proposed what is generally known as the "functional theory of Pommer." Instead of accepting the idea that the primary lesion in the joint is a degeneration of the cartilage or osteoporosis of the subchondral bone, he concluded that the first thing that happens is damage to the cartilage from trauma, with a loss of its elasticity, or that, if the cartilage has lost its elasticity as a result of the process of involution, it is more readily injured. When the elasticity of the cartilage is lost, the subchondral bone and its marrow are no longer protected from the irregular, localized effects of weight, pressure and impacts. This lack of protection and the subsequent trauma cause increased vascularization and ossification of the bone, with thickening and all the characteristic changes of degenerative arthritis. This theory of the development of degenerative arthritis has attracted widespread attention and interest, and there is ample clinical and experimental evidence available at present to support it. A few of the relevant facts are recalled.

There are numerous clinical examples of degenerative arthritis following trauma to the joints, with resulting incongruities of surface, static defects, abnormal weight bearing and pressure. A few of the more important ones may be cited.

When arthritis follows direct injury to a joint it is commonly called traumatic arthritis. When this occurs the clinical and pathologic features of the changes produced are sometimes indistinguishable from definite cases of degenerative arthritis in which no violent injury has occurred. For example, compressed fractures of one or both condyles of the tibia, with resulting genu valgum or varum, are invariably followed by changes in the knee joint characteristic of degenerative arthritis. In these cases the abnormal distribution of weight on one or the other tibial condyle, together with displacement of the patella, causes degenerative changes. Another example of such an occurrence is arthritis of the elbow joint developing as a result of fractures of the head or neck of the radius, with displacement of the head. If the displacement is not corrected or if the fractured bone is not removed, arthritis always appears sooner or later.

A further example of arthritis developing after an injury is its appearance following Legge-Perthes' disease or osteo-arthritis deformans juvenilis. As a result of the extensive researches of Lang¹⁸ and the

18. Lang, F. S.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, *J. Bone & Joint Surg.* **14**:563, 1932.

recent studies of Freund¹⁹ and of Miltner and Hu,²⁰ there seems to be little doubt that this disorder of the hip joint occurs as a result of direct or indirect traumatic damage to the cartilage, particularly at the osteochondral junction. This seems to be particularly striking if the blood supply through both the ligamentum teres and the periosteum is interfered with at the same time. The histologic picture is not unlike that seen in adults with osteo-arthritis of the hip joint, and with healing the deformity of coxa vara is commonly observed. The sequence of events in the healing of the process has recently been studied in detail by means of the roentgen ray by Freund.¹⁹ Key²¹ called attention to the deformity of the hip joint following the slipping of the upper femoral epiphysis in adolescence. In these cases the head of the femur is displaced so that it no longer forms a perfect ball and socket joint, and sooner or later, usually in adult life, pain and limitation of motion in the hip appear as a result of the changes following the mechanical defect.

Fractures of bones other than the ones mentioned may be followed by arthritis, for example, arthritis of the ankle joints following fracture of the os calcis and arthritis of the wrist joint following fractures of the lower end of the radius.

Arthritis following an injury to the hip joint may be seen in cases of posttyphoid coxitis. It is well recognized that when typhoid fever is complicated by arthritis the spine and hip are most commonly involved. When the hip is affected, subluxation or partial dislocation frequently occurs. This leads to a deformity of the head of the femur and acetabulum, and changes not unlike those seen in degenerative arthritis follow.

Charcot's Joints.—The alterations in so-called Charcot's joints must be regarded as nothing more or less than the results of frequent traumas to joints which have been rendered insensitive to pain by loss of the sensation of pain and the sense of position. There is overwhelming experimental and clinical evidence to support this view. The excellent review of the clinical aspects of the lesions in the joints caused by nerve lesions, as detailed by Shands,²² and the recent thorough histologic study of Charcot's joints by Moritz²³ leave no doubt that the lesions are

19. Freund, E.: Zur Deutung des Röntgenbildes der Pertheschen Krankheit, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **42**:435, 1930.

20. Miltner, L. J., and Hu, C. H.: Osteochondritis of the Head of the Femur; An Experimental Study, *Proc. Soc. Exper. Biol. & Med.* **30**:416 (Jan.) 1933.

21. Key, J. A.: Traumatic Arthritis and the Mechanical Factors in Hyper-trophic Arthritis, *J. Lab. & Clin. Med.* **15**:1145, 1930.

22. Shands, A. R., Jr.: Neuropathies of the Bones and Joints, *Arch. Surg.* **20**: 614 (April) 1930.

23. Moritz, A. R.: Tabische Arthropathie, *Virchows Arch. f. path. Anat.* **267**:746, 1928.

the result of repeated trauma to the joints. It should be emphasized that in many instances the changes in the joints are extensive owing to the excessive trauma that follows the loss of the sensation of pain. It is only natural to find less extensive changes following trauma to a joint in a person with intact sensation of pain for the reason that once the joint has been injured it is not used so much as a joint devoid of the sensation of pain. In some cases the changes produced by trauma are further exaggerated by a secondary invasion of the joint by bacteria. This occurs particularly if there are decubitus ulcers around the joints, such as the ankle joints.

Hemophilia.—One of the outstanding features of hemophilia is hemorrhage into the joints. This commonly follows slight trauma. Keefer and Myers²⁴ have emphasized that the changes brought about by repeated trauma and hemorrhage into the joints in patients with hemophilia were often indistinguishable from those of degenerative arthritis. In these cases, there is little doubt that the influences of the hemorrhage resulting from slight injury are capable of producing the derangements of the joints.

Aside from these clinical observations, there are a number of carefully controlled experiments on animals which support the hypothesis that degenerative arthritis results from frequent traumas to opposing articular surfaces. They are reviewed briefly.

Experimental Degenerative Arthritis.—Numerous attempts have been made to reproduce the gross and microscopic changes of degenerative arthritis in animals. A variety of methods have been used, but the favorite ones have been those which damage the cartilage and subchondral bone. Other methods, such as the production of a decreased blood supply and of increased pressure on the surfaces of the joints, and the displacement of articular surfaces so that they are no longer mutually adapted to one another have been employed.

The most recent work in America has been done by Key²¹ and by Bennett, Bauer and Maddock.²⁵ They studied the changes in the joints following the production of defects in the articular cartilage and noted alterations which were similar to those occurring in degenerative arthritis. Bennett, Bauer and Maddock were able to produce this picture with absolute regularity only when the patella became displaced following operation. When the defects in the cartilage of the femur were produced and the patella did not become displaced, the joints

24. Keefer, C. S., and Myers, W. K.: Hemophilic Arthritis, *New England J. Med.* **208**:1183 (June 8) 1933.

25. Bennett, G. A.; Bauer, W., and Maddock, J. J.: A Study of the Repair of Articular Cartilage and the Reaction of Normal Joints of Adult Dogs to Surgically Created Defects of Articular Cartilage; "Joint Mice" and Patellar Displacement, *Am. J. Path.* **8**:499, 1932.

remained essentially normal, except for the area damaged by the operation. These experiments are of the highest importance in showing the effect of incongruities of articular surfaces in producing degenerative arthritis. Other observers, notably, Axhausen²⁶ and Ely and Cowan,²⁷ produced changes in cartilage and bone similar to those seen in degenerative arthritis by destroying the cartilage with chemicals or with a knife. In some cases border exostoses were produced, but never with regularity. Other forms of trauma, such as freezing the joints and injury by percussion with a rubber hammer, have been used to produce arthritic changes in the joints, with reasonable success.

The effect of abnormal pressure on articular surfaces has been investigated by Müller.²⁸ He sutured the humeri of rabbits to the scapula and immobilized the shoulder so that the tendon of the biceps was in contact with the cartilage of the humerus. The result of these experiments was an erosion of the cartilage and changes in the bone caused by pressure. He did not observe the characteristic alterations of degenerative arthritis and concluded that the functional factors involved in movement following trauma were of importance in the production of lesions. When he produced loosening of the epiphysis and subluxation of the head of the femur in different animals a necrotizing and repair process on the head of the femur appeared, with the typical findings of degenerative arthritis.

Key²¹ tested the effect of abnormal strain on joints by attempting to produce knock-knee in rabbits. In the animals in which the patella was displaced outward so that it rested on the femoral condyle chronic arthritis developed, with border exostoses. In these animals other disturbances than displacement of the patella had been produced during the manipulations; the lower end of the femur had been fractured, the epiphysis had slipped or the cruciate ligaments had been torn. In other words, damage to the joints as well as the mechanical strain produced by the lack of mutually adapted articular surfaces were important in producing the picture.

Aside from the fact that trauma, mechanical strain and surface irregularities are essential for the experimental production of arthritic changes in the joints, movement of the damaged joint is of the highest importance in determining the anatomic picture. This feature has been investigated at length by Burckhardt.²⁹ He injured the cartilage of

26. Axhausen, Georg: *Arch. f. klin. Chir.* **99**:519, 1912.

27. Ely, L. S., and Cowan, J. F.: *Bone and Joint Studies*, Stanford University, Calif., Stanford University Press, 1916, p. 38.

28. Müller, W.: *Experimentelle Untersuchungen über Druckusuren an Gelenkenden für die Pathogenese der Arthritis deformans*, *Deutsche Ztschr. f. Chir.* **180**:203, 1923.

29. Burckhardt, H.: *Experimentelle Untersuchungen über die Beziehungen der Gelenkfunktionen zur Arthritis deformans*, *Arch. f. klin. Chir.* **132**:706, 1924.

the joints with phenol and studied the changes which developed in those which were immobilized by paralysis of the extremities by cutting the nerve plexus; he compared them with joints which were similarly injured but which were allowed to move. The final picture was different. In the joints which were immobilized the cartilage was gradually replaced by connective tissue and new cartilage which tended to fill the joint cavity and produce ankylosis. The connective tissue (pannus) grew into the articular space from the periphery of the joint, and exostoses were never observed. In the joints which were not immobilized exostoses developed, and the picture was similar to that seen in typical degenerative arthritis.

The experiments of Müller, cited previously, likewise emphasize the importance of movement in producing the characteristic changes in the joints. As he never produced characteristic lesions in immobilized joints he emphasized the importance of the functional aspect of disease of the joints.

In view of these observations, it seems well established that the lesions of degenerative arthritis may be reproduced in animals by a variety of methods which injure cartilage and bone and alter normal articular function. The picture which is characteristic of degenerative arthritis, then, is the result of the process of repair to damaged tissues of the joint.

From our observations and from those of other investigators, it seems difficult to escape the conclusion that the changes which are seen in the joints with increasing frequency with advancing age are identical with those which have been previously described as characteristic of degenerative arthritis. If this is true, there is justification for the belief that degenerative arthritis is a process associated with the aging of the tissues of the joints. This conception is essential for a complete understanding of the pathogenesis of this disorder. Added to the process of involution, such factors as gross trauma, hemorrhage and static deformities exaggerate the condition. The end-result depends on the summation of these factors.

SUMMARY AND CONCLUSIONS

In a study of 100 knee joints from 77 consecutive patients who died of various diseases the following facts were determined:

1. Anatomic changes were noted with increasing frequency with advancing age.
2. The patella showed alterations in 81 per cent of the cases, the interpatellar groove in 65 per cent, the lateral condyle of the tibia in

64 per cent, the medial condyle of the tibia in 55 per cent, the medial condyle of the femur in 43 per cent and the lateral condyle in 36 per cent.

3. The erosions were commonest over the areas of contact which were subjected to the greatest movement, strain, weight-bearing and injury.

4. The changes were identical in males and females, and there was no relationship between the extent of the lesions in the joints and the symptoms referable to the joints.

5. There was no correlation between the lesions in the joints and the degree of arteriosclerosis or any other particular type of disease process.

6. The gross anatomic changes were indistinguishable from those previously described in degenerative arthritis.

7. The various factors which are of importance in the development of degenerative arthritis are discussed. They include the aging of tissue, wear and tear, strain, trauma, occupation and static deformities.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

III. HEMOGLOBIN AND CELL VOLUME COEFFICIENTS; ERYTHROCYTE VOLUME, HEMOGLOBIN CONTENT AND CONCENTRATION; COLOR, VOLUME AND SATURATION INDEXES

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Innumerable articles about the anemia of pregnancy have been published, but, although these reports presuppose a knowledge of the normal changes in the blood incident to pregnancy, so far as we know, complete hematologic studies made on the same women throughout pregnancy are not available. Therefore, as a preliminary to an investigation of the true anemia of pregnancy, we made serial hematologic studies of the blood of the same women during pregnancy and the puerperium.

Haden,¹ Osgood and Haskins,² Wintrobe³ and others have determined the variations and averages in normal nonpregnant women. Their work demonstrates that the average erythrocyte has a definite volume and a definite content of hemoglobin, and that the hemoglobin forms a definite proportion of the cell. They discussed the importance of the color index, but stated that in addition the volume and saturation indexes together with the data for the average cell are of the utmost importance in a study of the blood. They stated that the volume index in pernicious anemia may be much greater in the early stages, when the count is relatively high, than in the later stages, when the count is low, thus indicating its value as an early diagnostic test.

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From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital, the Department of Obstetrics and Gynecology, the University of Chicago, and the Chicago Lying-in Hospital and Dispensary.

1. Haden, R. L.: The Value of Volume Index in the Diagnosis of Pernicious Anemia, *J. A. M. A.* **83**:671 (Aug. 30) 1924.

2. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women; Redeterminations of Color Index, Volume Index and Saturation Index Standards Based on Observations in One Hundred Cases, *Arch. Int. Med.* **39**:643 (May) 1927.

3. Wintrobe, M. M.: Blood of Normal Young Women Residing in Subtropical Climate, *Arch. Int. Med.* **45**:287 (Feb.) 1930.

The relationship between the absolute cell determinations and the three indexes is best shown, graphically, by Wintrobe.

$$\frac{\text{Volume (cc. per 1,000 cc.)}}{\text{R. B. C. (in millions)}} = \frac{\text{Corpuscular volume in cc.} \times 10^{-12} \text{ or cubic microns (c.}\mu\text{.)}}{\text{R. B. C. per cent}} \quad \left| \quad \frac{\text{Volume per cent}}{\text{R. B. C. per cent}} = \text{Volume index} \right.$$

$$\frac{\text{Hemoglobin (Gm. per 1,000 cc.)}}{\text{R. B. C. (in millions)}} = \frac{\text{Mean corpuscular hemoglobin in Gm.} \times 10^{-12} \text{ or micromicrograms (}\gamma\gamma\text{)}}{\text{R. B. C. per cent}} \quad \left| \quad \frac{\text{Hemoglobin per cent}}{\text{R. B. C. per cent}} = \text{Color index} \right.$$

$$\frac{\text{Hemoglobin (Gm. per 100 cc.} \times 100\text{)}}{\text{Volume (cc. per 100 cc.)}} = \frac{\text{Mean corpuscular hemoglobin concentration \%}}{\text{Volume per cent}} \quad \left| \quad \frac{\text{Hemoglobin per cent}}{\text{Volume per cent}} = \text{Saturation index} \right.$$

It is evident from the nature of these equations that all indexes must approximate unity in normal persons. The standard blood contains 14.3 Gm. of hemoglobin and 43 cc. of packed cells for each hundred cubic centimeters of blood and 5 million erythrocytes per cubic millimeter. These figures were derived from a study of one hundred women by Osgood and Haskins, and of fifty women by Wintrobe; the results were essentially the same (hemoglobin, 14.2; cells, 42.8). The variations of the indexes from unity, according to Haden, seldom exceed 5 per cent in normal adults. The color index in primary anemia is usually greater and seldom less than unity, while in secondary anemias from any cause it is lower. Haden, Osgood,⁴ Wintrobe, and others claimed that the volume index is a more accurate criterion of the types of anemia and stated that greater diagnostic information can be gained by a comparison of all three indexes. Peters and Van Slyke⁵ stated that the saturation index is of doubtful value in differentiating anemias because it is dependent partly on total electrolyte concentration and partly on the reaction or bicarbonate content of the blood.

Serial blood volume, hemoglobin, hematocrit and erythrocyte determinations were made on a group of women, designated as series A, beginning in the first trimester of pregnancy and continuing up to two weeks post partum. Another group, on whom the first determinations were made at term but continued up to eight weeks post partum, is designated as series B. In addition, groups of patients were studied at the different periods of pregnancy and the puerperium.

The methods which have been described in previous articles are all standard, and the accuracy is as great as is feasible. Hemoglobin,

4. Osgood, Edwin E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standard; Redeterminations Based on Findings in One Hundred and Thirty-Seven Healthy Young Men, *Arch. Int. Med.* **37**:685 (May) 1926.

5. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

hematocrit and erythrocyte determinations were converted to percentage of normal (hemoglobin, 14.3; hematocrit, 43; erythrocytes, 5 million) before the indexes were calculated.

In table 1 are listed the variations and averages for the color index. There is a small increase in the average color index during pregnancy, with a decrease at term and a still further decrease post partum. However, the entire change is within the normal variation. The wide range from 0.80 to 1.44 in normal pregnant or puerperal women indicates that one must be cautious in the diagnosis of anemia during pregnancy. This increase in the color index, which is best shown in the individual cases in table 4, indicates an increase in the hemoglobin, which may be

TABLE 1.—*Color Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89.....	..	1	3	7	4	6	2
0.90-0.99.....	7	..	2	15	2	12	3
1.00-1.09.....	7	7	4	15	6	9	5
1.10-1.19.....	7	1	10	11	10	6	1
1.20-1.29.....	4	..	4	2	1	3	..
1.30-1.44.....	2	3	2	4	..
Total.....	25	9	25	53	25	40	11
Averages							
Total cases.....	1.07*	1.04	1.10	1.04	1.07	1.04	0.97
Series A.....	1.07	1.08	0.98	1.01
Series B.....	1.00	0.99	0.96

* The normal range was from 0.90 to 1.10.

either absolute or relative. The former is unlikely, while the latter necessitates an increase in the size of the cell, which does occur.

In table 2 are listed the variations and averages for the volume index. The averages indicate an increase in the size of the cell during pregnancy and a decrease at term, with a still further decrease post partum. The wide range again indicates that caution must be used in the interpretation.

In table 3 are listed the variations and averages for the saturation index. These figures show marked variation, but a less wide digression from unity. This index of approximately 1 indicates that the hemoglobin content is only relatively increased.

In table 4 are listed the variations and averages for the individual cell volume in cubic microns. The volume remains within normal limits, but it is clearly evident that there is a definite increase in the size of the cell, reaching a maximum at from twenty-six to thirty-five weeks,

TABLE 2.—*Volume Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89.....	1	2	..	1	2
0.90-0.99.....	6	2	3	9	5	9	3
1.00-1.09.....	11	5	6	23	7	16	6
1.10-1.19.....	6	2	13	17	7	10	..
1.20-1.29.....	1	..	3	1	4	3	..
1.30-1.44.....	1	1	2	..
Total.....	25	9	25	53	24	41	11
Averages							
Total cases.....	1.07*	1.05	1.11	1.05	1.10	1.02	0.98
Series A.....	1.04	1.10	1.04	1.09
Series B.....	1.04	1.04	0.96	0.98

* The normal range was from 0.90 to 1.10.

TABLE 3.—*Saturation Index: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 to 17 Weeks
0.80-0.89.....	..	2	3	7	2	6	1
0.90-0.99.....	13	2	5	22	10	19	4
1.00-1.09.....	8	4	19	23	12	17	6
1.10-1.19.....	5	1	..	4	..	2	..
Total.....	26	9	27	56	24	44	11
Averages							
Total cases.....	1.02*	0.99	0.99	0.99	1.12	0.98	0.99
Series A.....	1.04	0.99	0.95	0.95
Series B.....	0.96	0.95	0.93	0.99

* The normal range was from 0.90 to 1.10.

TABLE 4.—*Individual Cell Volume, Cubic Microns: Variations and Averages in Pregnancy and the Puerperium*

	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
Cubic Microns								
70- 79.....	1	4	2	1	2	3
80- 89.....	12	4	6	24	8	14	3	5
90- 99.....	10	4	14	20	9	7	3	3
100-109.....	2	1	3	4	5	5	2	..
110-120.....	1	1	..	2
Total.....	25	9	24	53	24	29	10	11
Averages *								
Total cases.....	90.0†	89.5	94.0	90.3	93.8	91.3	90.1	84.2
Series A.....	89.9	94.0	89.2	..	93.6
Series B.....	88.6	89.1	82.0	84.1

* The normal average was 88.2 cubic microns.

† The normal range was from 80 to 100 in 24 patients.

a slight decrease at term and a still further decrease post partum. All changes, however, are within the normal limits.

In table 5 are listed the average hemoglobin and volume coefficients and the erythrocyte volume and hemoglobin content, both in grams and in percentage values, for series A and B. These coefficients are obtained with the following equations:

$$\text{Hemoglobin coefficient} = \frac{\text{hemoglobin} \times 5}{\text{R. B. O. (in millions)}} = \text{grams of hemoglobin per 5 million cells}$$

$$\text{Volume coefficient} = \frac{\text{hematocrit} \times 5}{\text{R. B. O. (in millions)}} = \text{cc. of cells per 5 million cells}$$

These data indicate that in the period of from ten to thirty-five weeks the erythrocytes differ from the average normal in that they are a little

TABLE 5.—Average Hemoglobin and Volume Coefficients and Corpuscular Volume and Hemoglobin Content for Series A and B During Pregnancy and the Puerperium

	Ante Partum, Weeks				Post Partum		
	10 to 15	26 to 35	36 to Term		10 to 25 Days		8 Weeks
	A	A	A	B	A	B	B
Hemoglobin coefficient, Gm. (Normal = 14.3)	15.5	15.7	14.2	14.2	14.6	13.4	13.8
Volume coefficient, cc. (Normal = 43.0)	45.1	47.3	44.9	44.5	47.1	41.8	42.3
Corpuscular:							
Volume, (c.μ.)..... (Normal = 88)	90.0	94.0	89.0	89.0	94.0	82.0	84.0
Hemoglobin 10 ⁻¹² , Gm. (Normal = 28.6)	30.4	29.7	28.6	28.5	27.2	26.9	27.7
Hemoglobin proportion, %.... (Normal = 32.5)	34.2	32.9	32.5	31.9	31.1	32.2	32.7

larger and contain more hemoglobin, and, as a result, the volume and hemoglobin coefficients are definitely increased. At term the various constants are essentially normal. At from ten to twenty-five days post partum, the figures for series A are essentially normal, with the exception of the cell volume, which is again increased. At eight weeks, the figures indicate a slightly smaller cell, with a normal concentration of hemoglobin, but a decreased amount, resulting in hemoglobin and volume coefficients which are also slightly decreased. An analysis of the data in this table indicates that there are marked changes in the erythrocytes in pregnancy, suggestive of a beginning primary anemia, especially between the tenth and the thirty-fifth week. The increase in the size of the cell between the twenty-sixth and the thirty-fifth week is probably a compensatory one, because the so-called physiologic anemia is greatest at this time.

In tables 6 and 7 are included essential data on series A and B. A detailed analysis of the results is unnecessary, but the individual varia-

TABLE 6.—Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Hemo- globin Coeffi- cient, Gm.	Volume Coeffi- cient, Cc.	Corpuscular			Indexes		
				Hemoglobin			Color	Volume	Satura- tion
				Volume, (c.m.)	10-12 Gm.	Proportion in Cell, %			
1	13 wks.	14.8	42.9	85	29.6	34.5	1.03	1.00	1.03
II	29 wks.	16.2	49.2	98	32.4	32.9	1.14	1.14	1.00
W	40 wks.	12.8	43.8	87	25.5	29.1	0.89	1.01	0.88
20	12 days	13.2	42.9	85	26.5	30.8	0.93	1.00	0.93
2	14 wks.	13.9	42.1	84	27.8	33.1	0.90	0.91	0.99
I	30 wks.	15.6	47.2	91	31.3	33.1	1.09	1.09	1.00
W	40 wks.	13.2	43.5	89	26.4	30.3	0.93	1.01	0.91
23	12 days	13.6	43.2	86	27.2	31.4	0.95	1.00	0.95
3	15 wks.	13.2	48.1	96	36.5	37.9	1.23	1.12	1.14
I	30 wks.	19.1	55.4	110	38.3	34.5	1.33	1.29	1.03
W	40 wks.	13.6	47.4	94	27.2	28.6	0.95	1.10	0.86
23	12 days	1.09
4	14 wks.	14.5	41.8	83	36.6	28.8	1.02	0.97	1.05
VII	27 wks.	14.8	42.9	85	33.8	34.5	1.03	1.03	1.03
W	40 wks.	0.99
30	14 days	13.2	44.6	89	31.8	30.0	0.92	1.03	0.88
5	12 wks.	16.0	46.5	92	31.2	34.5	1.12	1.09	1.03
II	28 wks.	15.0	45.9	91	27.0	32.6	1.05	1.06	0.99
W	39 wks.	13.3	44.4	89	25.7	30.0	0.93	1.02	0.91
25	14 days	12.3	48.2	96	20.1	25.5	0.86	1.11	0.77
6	14 wks.	14.0	44.3	88	25.7	31.7	0.99	1.04	0.95
I	27 wks.	16.0	48.7	97	25.7	32.9	1.13	1.13	1.00
W	40 wks.	12.5	38.8	77	32.2	32.1	0.88	0.91	0.97
19	11 days	16.7	45.8	91	33.4	36.4	1.16	1.06	1.09
7	14 wks.	17.4	53.2	106	24.6	32.8	1.22	1.24	0.99
VI	30 wks.	16.6	46.5	93	26.9	34.8	1.14	1.09	1.05
W	40 wks.	16.0	48.9	97	26.8	32.8	1.12	1.13	0.99
31	5 days	18.5	53.4	106	23.4	34.7	1.31	1.25	1.05
8	13 days	20.4	60.3	120	20.7	33.3	1.44	1.41	1.02
III	14 wks.	16.3	42.4	84	31.8	38.6	1.14	0.98	1.17
C	28 wks.	17.4	49.2	98	26.6	35.4	1.23	1.13	1.07
30	40 wks.	14.7	43.8	85	29.9	33.6	1.03	1.02	1.01
	11 days	11.9	40.0	80	23.8	30.0	0.84	0.93	0.91
9	14 wks.	14.4	46.4	92	28.8	31.1	1.00	1.03	0.93
I	29 wks.	16.8	47.5	94	33.5	35.3	1.17	1.10	1.07
C	40 wks.	14.7	46.6	93	29.4	40.8	1.02	1.07	0.95
21	3 days	15.6	47.5	95	31.3	32.9	1.10	1.10	1.00
	12 days	16.5	50.1	100	32.9	32.9	1.14	1.17	0.98
10	20 wks.	16.5	46.1	92	31.8	34.5	1.05	1.07	0.98
I	36 wks.	16.5	44.8	89	33.0	36.8	1.14	1.04	1.10
W	3 days	17.3	47.8	95	34.7	36.3	1.17	1.11	1.05
26									
11	15 wks.	16.7	49.4	96	33.3	34.4	1.16	1.13	1.03
I	28 wks.	12.9	44.1	88	25.8	29.2	0.91	1.03	0.83
W	39 wks.	13.3	43.1	86	26.5	30.8	0.93	1.01	0.92
22	12 days	15.6	51.9	103	31.1	30.0	1.02	1.20	0.85
12	9 wks.	14.0	38.5	76	28.0	36.3	0.92	0.89	1.03
I	27 wks.	11.0	41.6	83	22.0	26.5	0.76	0.96	0.79
C	40 wks.	15.0	44.1	88	29.9	33.9	1.04	1.02	1.01
28	11 days	12.5	43.1	86	24.9	28.9	0.88	1.00	0.83
13	11 wks.	36.4	1.09
VII	29 wks.	15.6	50.7	101	31.2	30.8	1.10	1.18	0.93
C	40 wks.	15.1	49.5	98	30.2	30.6	0.96	1.15	0.83
37	11 days	32.9	0.99
22	16 wks.	16.9	48.9	97	33.7	34.5	1.14	1.16	0.93
II	28 wks.	17.1	47.1	94	34.3	36.4	1.20	1.10	1.03
W	40 wks.	32.1	0.97
24	12 days	32.3	0.93

* W denotes white race; C, colored race.

tions during pregnancy are so marked that it is evident that a diagnosis of anemia requires more than a hemoglobin or erythrocyte determination and that, even with a complete hematologic examination, in many cases the diagnosis will still be questionable.

TABLE 7.—Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Hemo- globin Coeffi- cient, Gm.	Volume Coeffi- cient, Cc.	Corpuscular			Indexes		
				Hemoglobin			Color	Volume	Satura- tion
				Volume, (c.μ.)	10-12 Gm.	Propor- tion in Cell, %			
31	39 wks.	13.3	42.2	84	26.6	31.5	0.93	0.99	0.95
I	12 days	13.6	41.5	83	27.3	32.9	0.95	0.97	0.98
C	8 wks.	15.4	44.2	88	30.7	34.8	1.07	1.02	1.05
15									
32	40 wks.	16.1	49.1	98	32.2	32.8	1.12	1.15	0.98
I	3 days	16.6	48.6	97	33.1	34.1	1.15	1.12	1.03
W	12 days	12.0	41.7	83	24.1	28.9	0.84	0.98	0.86
27	8 wks.	13.6	39.3	78	27.1	34.5	0.94	0.91	1.03
33	40 wks.	16.6	48.2	96	33.1	34.4	1.17	1.12	1.04
II	3 days	14.3	42.9	85	28.6	33.3	1.00	1.00	1.00
W	19 days	13.1	39.3	78	26.2	33.3	0.91	0.91	1.00
29	9 wks.	14.8	41.9	83	30.0	35.3	1.04	0.98	1.06
34	40 wks.	16.1	44.4	88	32.2	36.3	1.12	1.03	1.09
I	5 days	14.0	40.6	81	28.1	34.5	0.98	0.95	1.04
C	8 wks.	14.0	45.6	91	28.0	30.8	0.93	1.06	0.92
25									
35	36 wks.	13.2	44.1	88	26.5	30.0	0.93	1.02	0.91
II	11 days	13.2	39.7	78	26.8	33.1	0.80	0.80	1.00
W	8 wks.	12.9	42.4	84	25.9	30.5	0.90	0.93	0.92
24									
36	40 wks.	12.4	42.8	85	24.9	29.1	0.87	0.99	0.88
I	3 days	10.4	39.0	78	20.7	26.5	0.72	0.90	0.80
C	12 days	13.2	40.2	80	26.4	32.8	0.92	0.94	0.98
25	8 wks.	10.0	35.5	70	20.0	28.3	0.70	0.82	0.85
37	38 wks.	12.6	43.4	86	25.2	28.9	0.89	1.01	0.88
III	12 days	12.2	43.3	86	24.4	28.2	0.86	1.01	0.85
W	8 wks.	12.0	38.1	76	24.0	31.4	0.84	0.88	0.95
30									
39	39 wks.	15.6	46.8	93	31.2	33.3	1.09	1.09	1.00
I	11 days	14.4	45.6	91	28.7	31.5	0.95	1.06	0.90
W	17 wks.	15.1	43.8	87	30.2	34.5	1.05	1.02	1.03
17									
40	40 wks.*	12.5	41.0	82	25.1	30.6	0.86	0.95	0.92
III	3 days	15.1	46.1	91	30.3	32.9	1.00	1.08	0.93
C	25 days	14.8	40.9	81	29.5	36.4	1.02	1.06	1.08
28	8 wks.	15.3	46.1	92	30.6	33.2	1.02	1.07	0.95
43	38 wks.	14.0	43.2	86	27.9	32.3	0.98	1.01	0.97
I	5 days	16.3	51.8	103	32.7	31.5	1.10	1.20	0.92
C	19 days	14.4	43.8	87	28.8	32.9	0.95	1.02	0.93
17	8 wks.	15.3	46.0	92	30.5	33.2	1.06	1.06	1.00

* W denotes white race; C, colored race.

CONCLUSIONS

Calculations of the various indexes, coefficients and absolute cell determinations of the blood during pregnancy and the puerperium indicate: 1. There are marked individual variations of all the indexes, especially of the color index, but the average for each remains close to unity.

2. The corpuscular volume is increased slightly between the twenty-sixth and the thirty-fifth week, when the anemia is at its maximum. There is another slight increase during the first week post partum, when a slight anemia is also present.

The hemoglobin and volume coefficients are increased during the greater part of pregnancy, but they are essentially normal at term and during the puerperium.

The corpuscular hemoglobin is increased slightly both in amount and in percentage during the greater part of pregnancy, but it is normal at term and during the puerperium.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

IV. PERCENTAGES AND GRAMS PER KILOGRAM OF SERUM PROTEIN AND FIBRIN AND VARIATIONS IN TOTAL AMOUNT OF EACH

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Many reports of changes in serum protein and fibrin in pregnancy have been published, but a study of the data indicates that the results are not uniform. The majority of the reports indicate that there is a decrease in serum protein and an increase in fibrin. Serial determinations of these substances on the same women throughout pregnancy and the puerperium should definitely demonstrate the direction and degree of change. Furthermore, the determination of the plasma volume on these same patients should make it possible to determine the total amount of serum protein and fibrin, the amounts per kilogram and the variations in total amount in each. Thus, the question of changes in protein in pregnancy would be settled, and some information as to the cause of the physiologic edema of pregnancy and of edema in general might be obtained.

In table 1 are listed some of the published data on the average percentages of serum protein and fibrin in nonpregnant and pregnant women (minimum figures for the latter). It is surprising to note the small number of patients used by the different investigators. With but two exceptions, all the reports indicate that in pregnancy the serum protein is decreased and the fibrin increased. The marked variations are due to the methods used. Refractometric determinations of protein yield high results unless the refraction of the nonprotein portion of each serum is also determined. This is done by the Robertson refractometric method, and the results can be compared with those obtained by the digestion method (Kjeldahl). The Wu method gives results which are relatively consistent and show the direction and degree of change, but cannot be compared with other methods because of inherent technical errors. The Kjeldahl method, in which the total and the

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TABLE 1.—Reported Averages for Percentage of Serum Protein and Fibrin in
Nonpregnant and Pregnant Women*

Year	Nonpregnant			Pregnant			Method
	Number of Patients	Serum Protein, per Cent	Fibrin, per Cent	Number of Patients	Serum Protein, per Cent, Minimum Average	Fibrin, per Cent, Maximum Average	
Rowe (Arch. Int. Med. 18: 455, 1916).....	22 H	7.50	Refractometric, Robertson
Linder, Lundsgaard and Van Slyke (J. Exper. Med. 39: 837, 1924)...	8	6.73	Macro-Kjeldahl
Salvesen (Acta med. Scandinav. 65: 147, 1926).....	16	7.02	Macro-Kjeldahl
Hove (Physiol. Rev. 5: 439, 1925).....	..	7.50	Macro-Kjeldahl
Peters et al. (J. Biol. Chem. 67: 141, 1926).....	15	6.59 P	Macro-Kjeldahl
Bruckman, D'Esopo and Peters (J. Clin. Investigation 8: 591, 1930)	8	7.61	Macro-Kjeldahl
Starlinger and Winands (Ztschr. f. d. ges. exper. Med. 60: 138, 1928)	16	7.78 P	0.25	Macro-Kjeldahl
Starlinger	Review	8.00 P	0.25	Refractometric, Relzz
Rowe	Review	7.94
Cameron (Textbook of Biochemistry, ed. 3, New York, The Mac- millan Company, 1931)	Review	6.7 to 8.2	0.30 to 0.60
Ifawck and Bergelm (Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931).....	Review	6.5 to 8.2	0.30 to 0.60
Zangemeister ³	2	8.15	6	6.32	Increased	Kjeldahl
Landsberg (Arch. f. Gynäk. 92: 693, 1910).....	8	7.01	18	6.54	0.44	Kjeldahl
Dienst (Arch. f. Gynäk. 109: 669, 1918).....	9	7.17	0.34	9	6.58	0.49	Kjeldahl, gravimetric
Mahnert ⁷	10	8.48	10	6.52	Refractometric, Relzz
Hafner (Arch. f. exper. Path. u. Pharmacol. 101: 335, 1924).....	6	Increased	Refractometric, Relzz
Plass and Bogert ^{6a}	22	7.04 P	88	6.27	Macro-Kjeldahl
Plass and Matthews ^{6c}	15	7.42 P	0.31	144	7.04	0.38	Wu method, colorimetric
Coetzee (Proc. Roy. Soc. Med. 18: 23, 1924).....	..	7.78 P	0.32	35	Reduced	0.52	Wu method, colorimetric
Kraul (Monatsschr. f. Geburtsh. u. Gynäk. 70: 6, 1925).....	0.25	50	6.50	0.50	Refractometric
Eufinger (Klin. Wehnschr. 7: 492, 1928).....	..	8.50	0.15	36	6.66	0.24	Refractometric, Relzz
Runge and Kessler (Arch. f. Gynäk. 126: 45, 1925)	24	8.70	44	No change	0.50	Refractometric, Relzz
Kydd (J. Biol. Chem. 91: 63, 1931).....	..	6.91	22	6.21	Macro-Kjeldahl
Gram (Acta med. Scandinav. 56: 106, 1922).....	25	0.29	57	0.55	Gravimetric
Foster (Arch. Int. Med. 24: 301, 1924).....	19	0.34	10	0.42	Gravimetric (ashed)

* In this table the following abbreviations are used: H = male and female; P = plasma (oxalate or citrate).

nonprotein nitrogen of the serum are determined and the difference multiplied by the constant, 6.25, gives the serum protein. This method requires 2 cc., but preferably 4 cc. (for duplicates) of serum for proper analysis and, at a minimum, forty minutes for a single determination. The interferometric method requires approximately 1 cc. of serum and from eight to ten minutes for an analysis. The last mentioned method, which is also used for the fibrin determination, is far more accurate than any of the others.

Another source of error is the use of plasma, which will give results that are too high because of the presence of fibrinogen, which, in pregnancy, may amount to 1 per cent or more. Furthermore, determination of plasma protein in which coagulation is prevented by means of oxalate, citrate or fluoride, also gives results which are too low, because the electrolyte causes the cells to shrink, thus squeezing out water which dilutes the plasma. This dilution may be great enough to make the serum protein actually higher than the plasma. For proper results, determinations should be made on serum, and the fibrin should be determined separately on plasma. Furthermore, the chief function of the serum protein is in the water exchange in the capillaries, and since fibrin is not concerned in this and has no measurable osmotic pressure, it should not be considered when speaking of serum protein.

The discussion of changes in serum protein in pregnancy, despite their importance in edema and toxemia, is limited in the obstetric textbooks. Thus, DeLee¹ stated:

The amount of fibrin and fibrinogen increases from the sixth month of pregnancy, and may be one-third greater than usual. This increase of fibrin is probably a conservative act of nature to prevent dangerous loss of blood during labor. Perhaps the hyperinosis causes the thromboses sometimes observed in the veins of the legs and pelvis even before labor.

Williams² stated:

Plass and Matthews, from the study of 314 women, showed that the total plasma protein decreases 9.3 per cent from the beginning of pregnancy to the ninth month, rises at the time of labor, and regains its original figure during the third week of the puerperium. At the same time its several fractions differ in their behavior; the albumin fraction diminishing, the globulin fraction remaining essentially stationary, while the fibrin increases, and attains its greatest height on the third day of the puerperium. Eufinger has approached the problem from a physico-chemical point of view, and by means of the refractometer finds that the plasma colloids undergo a characteristic and progressive change toward the large dispersal phase. In other words, coincident with a relative decrease in the total protein, he

1. DeLee, J. B.: *Principles and Practice of Obstetrics*, ed. 5, Philadelphia, W. B. Saunders Company, 1928.

2. Williams, J. W.: *Obstetrics*, ed. 6, New York, D. Appleton and Company, 1930.

finds an increase in the euglobulin and fibrinogen fractions. Both of these observations accord with the fact that the specific gravity of the blood is somewhat lowered, while the increase in fibrin may have some connection with the increased sedimentation rate of the blood in the latter part of pregnancy.

Zangemeister³ stated that the plasma in pregnancy is richer in water, but poorer in protein (a hydroplasmia). Fibrinogen is increased.

Seitz,⁴ in the Halban and Seitz series, concluded that there is a definite decrease in serum protein and a slight increase in water.

Denecke⁵ concluded that there is a hydroplasmia, but not a hydremia. He also reported an increase in fibrinogen.

Plass,⁶ after two separate investigations, concluded that the plasma proteins tend to be diminished, reaching a minimum at the sixth month during pregnancy and the early part of the puerperium. He stated that they are within the normal range at the end of the first week post partum. The fibrin rises during pregnancy to reach a high point shortly after delivery. The relative increase is greater than the absolute change. He pointed out that the existence of dilution of blood and plasma should be considered whenever studies of the blood are done during pregnancy, labor or the puerperium. This work by Plass and Bogert and by Plass and Matthews is the most extensive to date, but is based on analyses of oxalated plasma by the Kjeldahl method in the first report and by Wu's method in the second; the results, therefore, are of value in that they indicate the direction of change.

To summarize, a study of the reports in the literature indicates that the serum protein is decreased during pregnancy and that fibrin is increased, but the actual amount of change and whether or not the decrease in serum protein is primary or secondary to the increase in plasma volume are questions still open to discussion. If determinations of total protein were made, it would be possible to decide whether or not the decrease in the percentage of serum protein is due entirely to the increase in plasma. So far as we know, no one has investigated the changes in the total amount of fibrin in pregnancy.

Mahnert⁷ was the only investigator who determined plasma volume and serum protein per hundred cubic centimeters and then calculated the total grams of protein and the grams per kilogram. He stated that in

3. Zangemeister, W.: *Ztschr. f. Geburtsh. u. Gynäk.* **49**:92, 1903.

4. Seitz, L., quoted in Halban, Joseph, and Seitz, Ludwig: *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenburg, 1926, vol. 7, p. 654.

5. Denecke, G., quoted in Hinselmann: *Die Eklampsie*, Bonn, F. Cohen, 1924, p. 293.

6. (a) Plass, E. D., and Bogert, J.: *Bull. Johns Hopkins Hosp.* **35**:361, 1924; (b) *Am. J. Obst. & Gynec.* **6**:637, 1923; (c) Plass, E. D., and Matthews, C. W.: *ibid.* **12**:346, 1926.

7. Mahnert, A.: *Arch. f. Gynäk.* **114**:168, 1921.

the nonpregnant woman the maintenance of certain amounts of serum protein per kilogram is one of the fundamental physiologic necessities of the organism, and that, if calculated on a per kilogram basis, the serum protein in the pregnant woman is less than in the nonpregnant woman (0.56 per cent compared with 0.63 per cent), but that if the weight of the fetus and amniotic fluid is deducted, there is an actual increase in pregnancy. This increase in total protein is small, compared with the increase in blood volume.

Serial determinations of plasma volume, serum protein and fibrin were made on the same women at different periods of pregnancy and post partum. A similar study was started on patients at term and continued to eight weeks post partum. The first group is designated series A and the latter as series B. Additional data, not serial, were obtained on other women during pregnancy. All samples of blood were obtained in the morning and, whenever possible, from fasting patients. This is apparently of some importance so far as fibrin is concerned. Earle and Cullen⁸ noted that the fibrin clot was much larger if the blood was drawn after meals, with the exception of breakfast. Some unreported work of ours suggests that the ingestion of protein is associated with the increase in the size of the clot, as we have found a measurable increase in the fibrin after a meal containing protein.

METHOD

Plasma volumes were determined with congo red, as previously described. No stasis was used, and the blood was injected under oil into centrifuge tubes. The clot was broken up and the specimen centrifugated within twenty to forty minutes after the venipuncture. A longer or shorter time will affect the proteins, because, as the clot retracts, more water will be forced out of the cells, and the concentration of the proteins will be decreased. Serum protein and fibrin were determined with the interferometer. Approximately 1 cc. of serum and 1 cc. of plasma are required for the determinations. The method is far more accurate and less subject to errors than the refractometric method of Kjeldahl, or the colorimetric method of Wu.

RESULTS

In table 2 are listed variations and averages in serum protein throughout pregnancy and the puerperium. A normal range of from 5 to 8.9 per cent at once indicates the fallacy of studying different groups of patients in pregnancy. The standard deviations and the difference between the means for the various periods of the total cases have been calculated, and the latter figures indicate that the changes in the serum proteins

8. Earle, I., and Cullen, G.: *J. Biol. Chem.* 83:539, 1929.

are of no significance. However, the data for series A are of importance because the same patients were studied. These figures indicate a decrease of 6 per cent in pregnancy, and a still further decrease of 2 per cent during the first postpartum week, but then a rapid increase occurs, and at ten to fifteen days the serum proteins show an increase of 7 per cent and are slightly greater than when the patients were first seen. The decrease after delivery is probably due to an overcompensation of plasma volume for the concentration caused by labor, while the continued dilution, coincidental with the negative water balance, may be the result of the shift in water from the tissues (loss of physiologic edema). There is a constant increase after ten days, and at three weeks the

TABLE 2.—Percentage of Serum Protein: Variations and Averages in Pregnancy and in the Puerperium

Serum Protein, per Cent	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
5.0-5.4.....	5
5.5-5.9.....	1	5	7	2
6.0-6.4.....	6	6	17	26	5	9	3	1
6.5-6.9.....	11	4	6	21	5	13	1	4
7.0-7.4.....	5	1	2	3	3	5	5	4
7.5-7.9.....	1	1	1	1	..
8.0-8.4.....	1	..	1
8.5-8.9.....	1
Total.....	23	12	26	56	25	31	10	10
Mean								
Total cases.....	6.77 ± 0.06		6.42 ± 0.05	6.51 ± 0.04	6.13 ± 0.09	6.80 ± 0.07		
Standard deviation....	0.41		0.40	0.47	0.65	0.57		
Series A.....	6.76		6.55	6.36	6.11	6.85		
Series B.....	6.62	6.52	6.76	6.88	7.26

proteins are at the lower limits of normal. At eight weeks post partum they have increased 14 per cent above the term reading and are within the normal limits.

In table 3 are listed the variations and averages for serum protein calculated on a per kilogram basis. The plasma volume, multiplied by the per cent of serum protein, gave the total amount of circulating protein. This figure, divided by the weight, gave the amount of serum protein per kilogram. The determination of serum protein is an exact measurement, but the plasma volume is only approximate. However, since the determinations were made on the same patients, under similar conditions, the results are of value. Mahnert ⁷ made similar determinations. His report is based on a study of ten pregnant women on whom serum protein and plasma volume were determined with the refractometer. He stated that in the nonpregnant women the serum protein per kilogram ranged from 3.2 to 6.8 Gm., with an average of 6.3 Gm.,

while in pregnancy the range was from 3.1 to 8.5 Gm., with an average of 5.6 Gm. The maximum amounts were found in the last two months. If corrections are made for the weight of the fetus, placenta and amniotic fluid, there was an actual increase in pregnancy. The difference between the means for the various periods of the total cases has been calculated, and the figures indicate that the changes are of no significance. The amount of serum protein per kilogram is less than that reported by Mahnert;⁷ this is due, in all probability, to the following factors: He determined serum protein with the refractometer without filtrate determinations, which gives high readings. He used a refractometric method for determining the plasma volume; the foregoing criticism is also

TABLE 3.—*Serum Protein in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and in the Puerperium*

Grams per Kilogram	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	15 to 26	8 to 17 Weeks
2.0-2.4.....	5	1	2	3	6	1
2.5-2.9.....	5	1	8	16	8	14	2	2
3.0-3.4.....	7	6	11	22	6	6	2	3
3.5-3.9.....	5	2	3	12	3	6	3	3
4.0-4.4.....	2	1	2	2	2	2	1	1
4.5-4.9.....	2	2	1
Total.....	24	11	26	55	25	31	10	10
Means								
Total cases.....	3.13 \pm 0.09		3.15 \pm 0.07	3.20 \pm 0.04	2.99 \pm 0.05	3.25 \pm 0.05		
Standard deviation....	0.62		0.5	0.47	0.59	0.65		
Series A.....	3.03	3.28	3.09	2.99	2.83	3.50		
Series B.....	3.34	3.09	3.04	3.88	3.56

applicable to this method. Furthermore, his series is small. Mahnert stated in regard to the nonpregnant women that the maintenance of a certain definite amount of serum protein per kilogram is one of the fundamental physiologic necessities of the organism. The constancy of our figures indicates that this statement is also applicable to the pregnant women. Data on separate patients, which are given in tables 8 and 9, demonstrate this constancy even more clearly.

In table 4 are listed the variations and averages for the percentage of fibrin. In the total series there is an average increase of 20 per cent, which rises still higher during the first postpartum week, and then slowly falls to a figure usually found in early pregnancy. This increase at term is significant. Series A shows an increase of 10 per cent at term, with a slight increase at from ten to fifteen days. Series B shows an increase of 34 per cent in the first postpartum week, and then a gradual decrease to a figure which is still slightly high at eight weeks.

It does not seem to us that the increase during pregnancy is a protective mechanism, as many observers maintain, but it is more likely due to the invasion of the blood by protein elements (chorionic tissue). A high percentage of fibrin is found whenever foreign protein enters

TABLE 4.—*Percentage of Fibrin: Variations and Averages in Pregnancy and in the Puerperium*

Fibrin, per Cent	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.20-0.29.....	3	1	4	3	2	2
0.30-0.39.....	10	4	8	8	2	12	3	5
0.40-0.49.....	6	4	8	20	4	9	5	2
0.50-0.59.....	3	..	2	18	9	6	..	1
0.60-0.69.....	1	1	2	5	6	2	1	1
0.70-0.79.....	..	2	1	..	1
0.80-0.90.....	1	1	2
Total.....	23	12	26	55	26	31	9	9
Mean								
Total cases.....	0.40 ± 0.01		0.43 ± 0.02	0.48 ± 0.01	0.55 ± 0.02	0.43 ± 0.01		
Standard deviation....	0.10		0.15	0.12	0.15	0.10		
Series A.....	0.40		0.39	0.44	0.45		
Series B.....	0.47	0.63	0.41	0.42	0.43

TABLE 5.—*Fibrin in Grams per Kilogram of Body Weight: Variations and Averages in Pregnancy and in the Puerperium*

Grams per Kilogram	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 25	8 Weeks
0.10-0.19.....	16	5	12	13	3	20	4
0.20-0.29.....	6	4	10	30	15	16	4
0.30-0.39.....	2	1	3	9	6	3	1
0.40-0.49.....	..	1	1	2	..	1	..
0.50-0.54.....	1
Total.....	24	11	26	54	25	40	9
Mean							
Total cases.....	0.187 ± 0.005		0.219 ± 0.01	0.245 ± 0.007	0.269 ± 0.01	0.207 ± 0.008	
Standard deviation	0.064		0.081	0.075	0.081	0.073	
Series A.....	0.17		0.18	0.21	0.23	
Series B.....	0.27	0.30	0.20	0.21

the blood stream, as in cancer, infections and nephrosis (infection). Furthermore, the peak of the percentage of fibrin is post partum, when there is not the need for coagulation that there is at term, but when the wound surface (placental area and involution) is at its maximum.

In table 5 are listed the data on the grams of fibrin per kilogram. The calculations are similar to those used in determining the serum pro-

tein per kilogram. The mean figures show an increase of 33 per cent at term in the total cases, and of 23 per cent in series A. This increase at term is significant. There is a still further increase during the first week post partum and then a gradual decrease to a figure which is still higher than those found early in pregnancy.

TABLE 6.—Average Changes in Serum Protein and Fibrin Calculated from Variations in Total Amount Using the Initial Determination as 100 Per Cent for the Ante Partum Period

	Serum Protein		Fibrin	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 26 to 35 weeks of gestation:				
Average increase for all patients	18	13.7	18	23.2
Average increase for those showing increase	10	29.3	12	41.7
Average decrease for those showing decrease.....	4	13.3	3	26.0
No change	4	0	3	0
From 36 to 40 weeks of gestation:				
Average increase for all patients	15	18.3	15	40.0
Average increase for those showing increase.....	10	29.4	15	40.0
Average decrease for those showing decrease.....	2	12.0	0	0
No change	3	0	0	0

TABLE 7.—Average Changes in Serum Protein and Fibrin Calculated from Variations in Total Amount, Using the Last Ante Partum Determination as 100 Per Cent for the Post Partum Period

	Serum Protein		Fibrin	
	Number of Cases	Mass Change, per Cent	Number of Cases	Mass Change, per Cent
From 2 to 6 days post partum:				
Average decrease for all patients	25	16.6	25	5.0
Average decrease for those showing decrease.....	20	21.5	13	28.0
Average increase for those showing increase.....	1	17.0	9	26.3
No change	4	0	3	0
From 10 to 25 days post partum:				
Average decrease for all patients	41	4.6	40	11.7
Average decrease for those showing decrease.....	20	20.0	27	32.5
Average increase for those showing increase.....	12	17.6	8	50.9
No change	9	0	5	0
From 8 to 17 weeks post partum:				
Average decrease for all patients	10	7.4	9	25.7
Average decrease for those showing decrease.....	5	15.4	6	42.2
Average increase for those showing increase.....	2	6.5	2	9.5
No change	3	0	1	0

In table 6 are given data on the changes in total amount for serum protein and fibrin. The calculations are as follows: The total amount of serum protein for each period is calculated; the first reading in pregnancy is assumed to be 100 per cent, and all other readings up to and including those at term are divided by this first figure. Thus all the data are converted to per cent changes and can then be compared. Similar calculations were used for the fibrin. There is an average increase of 13.7 per cent in the serum protein at from twenty-six to

TABLE 8.—Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)*

Number, Gravidity, Color, Age	Period of Gestation or Post Partum	Weight	Serum Protein				Plasma Vol-ume Change, per Cent	Fibrin			
			Per Cent	Gm. per Kg.	Total Amt., Gm.	Change, per Cent		Change, per Cent	Total Amt., Gm.	Per Cent	Gm. per Kg.
			1	2	3	4	5	6	7	8	9
I	13 wks.	46.3	6.79	2.74	127	10.80	0.578	0.23
II	29 wks.	55.9	6.66	3.70	207	163	166	106	11.46	0.369	0.21
W	40 wks.	59.5	6.51	4.22	251	198	206	179	19.28	0.500	0.32
20	12 days	50.4	6.78	4.68	236	94	90	102	19.69	0.566	0.39
2	14 wks.	77.9	6.59	2.48	193	15.00	0.511	0.19
I	30 wks.	81.0	6.88	2.86	232	120	115	166	24.85	0.738	0.31
W	40 wks.	80.9	6.05	2.60	210	109	119	129	19.41	0.558	0.24
23	12 days	73.6	6.79	2.79	205	98	86	69	13.46	0.446	0.18
3	15 wks.	53.0	6.68	3.75	199	10.59	0.356	0.20
I	30 wks.	61.1	6.68	4.06	248	125	125	146	15.44	0.415	0.25
W	40 wks.	63.5	6.42	3.48	221	111	116	122	12.90	0.375	0.20
23	12 days	53.0	7.13	4.23	224	101	91	101	13.02	0.415	0.25
4	14 wks.	92.2	6.87	2.25	207	11.76	0.391	0.13
VII	27 wks.	91.7	6.83	2.74	251	121	122	139	16.33	0.445	0.18
W	40 wks.	87.0	5.83	2.68	233	113	133	112	13.12	0.328	0.15
30	14 days	82.7	6.71	2.43	201	86	75	80	10.52	0.352	0.13
5	12 wks.	53.6	7.01	2.80	150	9.59	0.449	0.18
II	28 wks.	59.5	7.17	3.33	198	132	129	98	9.43	0.342	0.16
W	39 wks.	60.0	6.66	3.32	199	133	140	180	17.22	0.576	0.29
25	14 days	52.5	7.02	4.91	258	130	123	90	15.45	0.420	0.29
6	14 wks.	45.9	6.34	3.05	140	6.96	0.316	0.15
I	27 wks.	54.8	6.08	3.07	168	120	116	130	9.02	0.327	0.16
W	40 wks.	63.5	5.58	2.72	173	124	141	190	13.23	0.426	0.21
19	11 days	56.0	6.49	3.38	189	109	94	116	15.33	0.527	0.27
7	14 wks.	107.2	6.88	2.22	238	14.09	0.408	0.13
VI	30 wks.	112.5	6.37	2.14	241	101	110	77	10.86	0.287	0.10
W	40 wks.	114.6	7.44	2.52	289	121	112	126	17.78	0.458	0.16
31	5 days	100.3	6.79	2.71	272	94	103	117	20.72	0.518	0.21
	13 days	100.4	6.66	3.28	329	114	127	86	15.36	0.311	0.15
8	14 wks.	92.9	7.08	3.29	306	20.34	0.471	0.22
III	28 wks.	103.5	7.12	2.71	281	92	92	95	19.39	0.491	0.19
C	40 wks.	108.9	6.89	2.72	296	97	100	106	21.51	0.500	0.20
30	11 days	100.0	85
9	14 wks.	50.0	6.50	3.26	163	5.10	0.204	0.10
I	29 wks.	55.8	6.13	3.30	194	119	127	139	7.10	0.224	0.12
C	40 wks.	60.0	6.31	3.40	204	125	129	185	9.41	0.291	0.16
21	3 days	55.8	6.12	3.33	186	91	94	102	9.57	0.314	0.17
	12 days	52.5	6.80	3.83	201	99	92	69	6.52	0.220	0.12
10	20 wks.	71.8	6.75	3.01	216	11.92	0.372	0.17
I	36 wks.	75.5	6.30	3.01	227	105	113	169	20.16	0.560	0.27
W	3 days	70.3	5.43	2.46	173	76	85	43	8.68	0.273	0.12
26											
11	15 wks.	67.2	6.24	3.20	215	13.31	0.387	0.20
I	28 wks.	73.8	6.20	2.95	218	101	102	124	16.56	0.471	0.22
W	39 wks.	76.5	6.22	2.86	219	102	102	108	14.38	0.409	0.19
22	12 days	68.1	6.95	3.36	229	105	94	141	20.22	0.613	0.30
12	9 wks.	61.3	7.40	3.72	228	13.69	0.445	0.22
I	27 wks.	80.0	6.36	3.26	261	114	133	102	14.03	0.342	0.18
C	40 wks.	86.3	6.42	2.33	201	88	102	110	15.12	0.432	0.18
28	11 days	75.6	7.32	2.98	225	112	97	111	16.79	0.546	0.22
13	11 wks.	68.1	6.76	3.55	242	8.23	0.230	0.12
VIII	29 wks.	75.4	6.33	3.20	241	100	106	122	10.06	0.264	0.13
C	40 wks.	71.5	6.02	2.99	214	88	99	132	10.84	0.305	0.15
37	11 days	65.6	6.73	3.38	222	104	93	170	18.47	0.560	0.28
22	16 wks.	55.7	6.59	3.55	198	6.45	0.215	0.12
II	28 wks.	64.3	6.30	2.80	180	91	95	171	11.03	0.386	0.17
W	40 wks.	67.5	6.07	0.420
24	12 days	60.8	6.48	2.81	171	8.88	0.336	0.15

* In this table, W indicates white race; C, colored race.

thirty-five weeks, and an average increase of 29.3 per cent in ten of the eighteen patients studied. Four showed a decrease of 13.3 per cent and four no appreciable change (5 per cent or less). At term the average increase for the serum protein was 18.3 per cent, and in ten of the fifteen patients studied, 29.4 per cent. Two showed an average

TABLE 9.—*Data on Patients Followed from Term to Eight Weeks Post Partum (Series B) **

Number, Gravida, Color, Age	Period of Gestation or Post Partum	Weight	Serum Protein				Plasma Vol- ume Change, per Cent	Fibrin			
			Per Cent	Gm. per Kg.	Total Amt., Gm.	Change, per Cent		Change, per Cent	Total Amt., Gm.	Per Cent	Gm. per Kg.
31	39 wks.	67.0	5.93	3.53	237	20.36	0.509	0.30
I	12 days	56.5	6.14	2.78	157	66	64	50	10.25	0.400	0.18
C	8 wks.	53.6	74
15											
32	40 wks.	65.0	6.12	3.14	204	13.50	0.405	0.21
I	3 days	58.0	5.60	2.48	144	71	77	103	13.84	0.537	0.24
W	12 days	55.5	6.38	3.15	175	86	82	81	10.94	0.399	0.20
27	8 wks.	60.5	6.80	3.06	185	91	82	66	8.86	0.325	0.15
33	40 wks.	103.4	6.74	2.52	261	13.38	0.345	0.13
II	3 days	90.0	6.98	2.94	265	102	98	181	24.24	0.638	0.27
W	19 days	87.5	6.33	2.50	219	84	89	100	13.33	0.386	0.15
29	9 wks.	89.2	6.94	3.14	280	107	104	107	14.29	0.354	0.16
34	40 wks.	72.2	6.58	3.28	237	20.59	0.572	0.29
I	5 days	68.1	5.88	2.42	153	65	78	85	17.50	0.674	0.28
C	8 wks.	64.5	7.28	3.58	231	97	88	55	11.28	0.356	0.17
25											
35	36 wks.	68.1	6.70	3.10	211	13.40	0.425	0.20
II	11 days	61.5	6.55	2.96	182	86	88	78	10.51	0.378	0.17
W	8 wks.	58.6	6.96	3.16	185	88	84	103	13.75	0.518	0.23
24											
36	40 wks.	68.4	8.40	3.89	266	20.86	0.660	0.30
I	3 days	63.0	7.40	4.03	257	97	110	76	15.86	0.456	0.25
C	12 days	56.8	8.30	3.98	226	85	86	67	13.91	0.511	0.24
23	8 wks.	54.5	8.95	5.19	283	106	100	65	13.60	0.430	0.25
37	38 wks.	82.0	6.35	3.78	310	14.74	0.302	0.18
I	12 days	73.0	6.72	2.68	106	63	60	69	10.10	0.346	0.14
W	8 wks.	75.0	7.21	4.00	300	97	85	112	16.54	0.398	0.22
30											
39	39 wks.	67.5	6.40	3.34	208	16.04	0.493	0.26
I	11 days	51.9	6.48	2.70	140	67	67	61	9.84	0.454	0.19
W	17 wks.	50.0	6.94	2.64	132	63	59
17											
40	40 wks.	54.0	6.64	3.61	195	26.70	0.910	0.49
III	3 days	48.2	6.60	3.86	186	95	96	96	25.69	0.910	0.53
C	25 days	46.8	7.12	4.44	203	107	100	49	13.02	0.445	0.28
28	8 wks.	47.2	7.14	3.64	172	88	82	60	16.01	0.665	0.34
43	38 wks.	72.2	6.33	3.25	235	25.01	0.674	0.35
I	5 days	63.5	6.70	2.77	176	75	71	57	14.14	0.537	0.22
C	19 days	62.2	7.19	4.71	293	125	110	72	18.02	0.442	0.29
17	8 wks.	61.9	7.09	3.63	225	96	86	53	13.14	0.414	0.21

* In this table, W indicates white race; C, colored race.

decrease of 12 per cent, and two showed no change. There was a marked increase in fibrin at from twenty-six to thirty-five weeks, but the most striking point was that all fifteen patients showed an average increase of 40 per cent at term.

In table 7 are given data on the changes in total amount after delivery. The calculations are similar, except that the reading at term

is assumed to be 100 per cent and all subsequent figures are divided by it. There is a definite decrease in serum protein after delivery, which is most marked in the first week. The fibrin shows a constantly increasing diminution, reaching a maximum decrease of 25.7 per cent at eight weeks, thus confirming the statement that there is an increase during pregnancy.

Table 8 lists essential data on the separate patients comprising series A. During pregnancy only one patient showed an increase of 8 per cent in serum protein at term, although at thirty weeks' gestation there had been a decrease of 7 per cent. All of the others had decreases, varying from 0.3 to 15 per cent. The average decrease was 7 per cent. There are variations of considerable magnitude in the grams of protein per kilogram, but the fact that there is some relatively constant figure for each patient indicates, we believe, that there is an optimum amount of serum protein which the body tends to keep constant. The figures for percentage of fibrin are very irregular, and although most of the patients showed some increase at term, the greatest increase was post partum. The total amounts of fibrin and also the grams per kilogram showed marked increases in pregnancy in all cases. The change in eight cases amounted to 50 per cent or more.

Table 9 lists essential data on the separate patients comprising series B. The increase of serum protein to within normal limits at eight weeks is evident. The values have not returned to normal at the end of the first week post partum, as stated by Plass and Bogert,^{6a} if studied individually or collectively. The percentage of fibrin and the number of grams per kilogram were variable, but were decidedly lower at eight weeks post partum. The decreases in total fibrin were just as great post partum as the increase had been during pregnancy in series A.

COMMENT

It is difficult to understand why the percentage of serum protein should decrease in pregnancy. Our study of the separate patients shows that the decrease is not nearly as great as heretofore believed. In fact, some might consider the change of no significance, but the decrease in most of the patients is much more than the error of the method, and, as we have demonstrated by bi-hourly studies, the percentage of serum protein is a constant entity; therefore, the decrease is significant.

The explanation heretofore given that the decrease in the percentage of serum protein is due to the watery dilution of the blood is untenable with the definite increase in total serum protein. One obvious explanation is that the body attempts to keep the serum protein constant as the plasma volume increases, and that it cannot compensate any closer than it does. However, we are finding changes in many of the impor-

tant constituents studied, and although they are not of the same magnitude, the direction of the change is, as a rule, the same. Therefore, it seems to us that there is a definite plan in the changes which, if solved, will throw considerable light on metabolism of water, on edema and on renal function both in health and in disease.

The changes in fibrin in pregnancy may be due to the stimulus produced by the constant breaking off of chorionic villi (deportation of Veit⁹). Mills¹⁰ has demonstrated that in vivo injections of tissue extract or extracellular fluid, which is comparable to the breaking off of a villus, at which time a minute amount of extracellular fluid is set free, produces a definite increase in fibrin. Figures for fibrin are especially high in eclampsia, in which the deportation, supposedly, may be at its maximum. The facts that fibrin is also markedly increased in cancer and in infection and that our figures are greatest after delivery make the theory improbable that the increase is a protective one for coagulation of the blood.

Our work also demonstrates the unreliability, at least, of chemical data obtained from various groups of women during pregnancy, especially if the substance being studied has a wide normal range.

CONCLUSIONS

The normal figures for serum protein and fibrin reported in the literature for both nonpregnant and pregnant women are based on a relatively small number of determinations, and the data on the latter are especially confusing, either because of the methods used or because serial determinations on the same women were not made.

Determinations of serum protein, fibrin and plasma volume were made on various patients for the different periods of pregnancy and the puerperium. The results were studied statistically, and the following conclusions were made:

1. The changes in percentage of serum protein and in amount of serum protein per kilogram of body weight are of no significance.

2. The changes in percentage of fibrin and in amount of fibrin per kilogram of body weight are significant. At term the former has increased 20 per cent and the latter 30 per cent.

A similar study in which the observations were made on the same women indicates that:

1. The serum proteins at term are from 0.3 to 15 per cent—average 7 per cent—below those of the first trimester. There is a still further

9. Veit, J.: *Die Verschleppung der Chorionzotten*, Wiesbaden, J. F. Bergmann, 1905.

10. Mills, C., and Guest, G.: *Am. J. Physiol.* **57**:395, 1921.

decrease the first few days post partum and then a slow rise, reaching a normal figure at about eight weeks post partum.

2. The amount of serum protein per kilogram remains rather constant during pregnancy, ranging from 2.5 to 3.5 Gm., with an average that is approximately 3.0 Gm. per kilogram.

3. Determinations of the total amount of serum protein indicate that there is an average increase of 14 per cent at from twenty-six to thirty-five weeks, and an increase of 18 per cent at term. The figures post partum are extremely variable, with the major portion of the patients showing a decrease which, after the first week, is almost negligible.

4. Figures for the percentage of fibrin show marked variations, but there is an average increase at term of 10 per cent. At eight weeks post partum the figures are still above normal.

5. The grams of fibrin per kilogram show a more marked increase during pregnancy, reaching a maximum during the first week post partum and then slowly decreasing, but at eight weeks the figures are still above normal.

6. Determinations of the total amount of fibrin indicate an average increase of 23 per cent at from twenty-six to thirty-five weeks, and an increase of 40 per cent at term. During the first week post partum there is a slight decrease amounting to 5 per cent, but at eight weeks the average decrease is 26 per cent, thus furnishing additional evidence that there had been an increase in pregnancy.

7. The decrease in serum protein, even if the loss were all albumin, is insufficient in itself to cause physiologic edema. Changes in the osmotic pressure, surface tension and base-binding power of the proteins out of proportion to the decrease seem to indicate that there are intrinsic alterations in the proteins themselves.

A COMPARISON OF THE DEVELOPMENT OF THE SPECIFIC NODULE OF SILICOSIS AND OF TUBERCULOSIS

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The earliest historians dealing with mining and the hazards of the industry as they affected the health of the miner have recognized a relationship between the various types of dust and the production of disease. They knew of corrosive and noncorrosive types of dust, both of which produced disability, the former causing such serious injury to the lung that death ensued. Because the sickness resembled what is now called tuberculosis, the term "dust phthisis" came into use. Many patients suffering from dust phthisis became emaciated, coughed productively, had fever and died. It has been reported that in the sixteenth century in the mining communities of the Carpathian Mountains many women could be found who had been widowed time after time by miner's phthisis. The exact relationship between the corrosive and noncorrosive dusts was slow in being established. Finally, however, in the early part of the nineteenth century, Alison, professor of medicine at Edinburgh, established the association between dust phthisis and tuberculosis, that is, between dust phthisis and true phthisis. It was not dust itself that was responsible for the "ulceratio" of Celsus but a secondary complication. The "corrosive dust" noted by Agricola in the sixteenth century and by Ramazzini in the eighteenth century became the "tuberculosis" of Alison. Fifty years ago, the bacillus of tuberculosis was discovered and added a final confirmation to Alison's work, and less than twenty years ago it was shown that the only dust of importance in the production of dust phthisis is silica. As a result, the term "silicosis" is being used to cover all forms of harmful pneumoconiosis.

The relationship between the noncorrosive and the corrosive forms of dusts was further emphasized when it was shown that one condition

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was uncomplicated by infective agents and produced "simple silicosis," whereas the other operated in association with infection and produced what is now termed "infective silicosis." The infection most commonly acting as a complication was proved to be set up by the bacillus of tuberculosis, and the degree of responsibility of each as an etiologic factor was expressed by the terms employed: "silicotuberculosis" and "tuberculosilicosis." These terms are intended to indicate which of the two was the primary and which the secondary or complicating factor.

The pathologic study of the lesions in simple silicosis further emphasizes the bond of similarity existing between the two diseases. Silica arrested in the lung produces nodules resembling those characteristically formed by the arrest of *Mycobacterium tuberculosis*. Its phthisis-producing capability is dependent on its relative inertness and insolubility. It is thus relatively indestructible and can remain indefinitely impounded within the lung. It is too inert seriously to injure the phagocyte that ingests it, and too inert to cause an exudative reaction that might facilitate its removal; yet, being slightly soluble in tissue juices and slightly irritant, it is able to encourage proliferation over a long period of time. Because silica is relatively inert, the injury produced depends on the number of particles arrested in the lung and on their intracellular reactions. This in turn depends on the size of the particles, which in order to permit of phagocytosis must be approximately that of a micro-organism.

Similarly, the reaction to the bacillus of tuberculosis depends on its relative inertness and indestructible characteristics. It is protected against destruction by its waxy envelop; it does not immediately destroy its cellular host but rather lives, grows and multiplies within the phagocytic cell; it does not immediately produce a highly exudative reaction unless it is present in great numbers or unless its host has been sensitized to it. Unlike silica, it is dependent neither on size nor on number for its effect. Silica must be in particles of less than 10 microns, and there must be as many as 10,000,000 particles in each cubic foot of air if characteristic nodules in the lung are to result from inhalation. If only few, the bacilli may cause nodules, and they are always of a size that is readily phagocytosed. They are alive and multiply, and the resulting injury is progressive. Silica is inorganic, incapable of multiplication, and the resulting injury may be self-limited.

METHOD OF STUDY

In order to observe and compare the reactions in tissue that resulted from invasion of these common and frequently associated irritants, we injected through a cannula introduced into the trachea, suspensions of particles of silica of suitable size and number in a series of normal rabbits. At the same time, we injected the same amount of a suspension of virulent bacilli of tuberculosis of avian type (*Mycobacterium avium*) into an equal number of normal rabbits. These animals

were killed in pairs at equal intervals of from five hours to four weeks. The resulting lesions were compared for gross and microscopic similarities and differences. The limit of four weeks for the duration of the experiment was chosen because we knew that under the conditions of the experiment the reactions of silica are completed within that length of time, and because we did not wish to be confused by the domination of inflammatory reactions consequent on reinfection of the tuberculous animals. It was obvious that the advantage in the method depended on the speed of the reaction induced when silica was used and on the certainty of producing an infection when employing the bacilli of tuberculosis. It was equally obvious that in the case of silica the disadvantage consisted in the added ease of its removal. Animals that were given injections of silica needed to be well under the influence of the anesthetic; if they were not, they rid their lungs of all particles, and a lesion did not result.

RESULTS

Reactions Due to Bacilli of Tuberculosis.—The first reaction of the lung to the introduction of the organism seemed to be entirely non-specific and in every way resembled that resulting from the introduction of such inert substances as graphite. The following occurred: a mild degree of atelectasis and an associated inflammation characterized by hyperemia, exudation of serum and an inrush of polymorphonuclear cells with the formation of an exudate within the bronchi, the bronchioles and the finest of their subdivisions. The wandering of polymorphonuclear cells could be determined, and their passage from the parenchyma into the bronchial lumen demonstrated. Also as a non-specific reaction of defense, phagocytosis took place and made the polymorphonuclear cells and the alveolar phagocytes conspicuous. It is certain that this mechanism is brought into operation almost instantly, and that the mononuclear cell or alveolar phagocyte is the more active of the two, although the polymorphonuclear cell exhibits phagocytosis and is present in far greater numbers. The next nonspecific defense mechanism consisted in the removal of the bacilli from the lung; this is accomplished by two means: The bronchial mechanism is effective and is made possible by the action of ciliated cells and a sensitivity of the mucosa resulting in the production of cough. The lymphatic system is effective as a drainage mechanism, as evidenced by the presence of bacilli within the regional nodes and even in the abdominal viscera within as brief a period of time as one hour. The effectiveness of the lymphatic system is made possible by the ability of the actively functioning phagocyte to wander throughout the parenchyma to those situations in which lymphatic vessels normally exist. Thence, these bacteria-laden cells are hurried outward toward the pleura or toward the hilus on their way to join the main lymphatic trunks. If it were possible for these mechanisms of defense to remove all bacilli and their products, no lesion would result. A lesion is made possible by retention within the lung of bacilli which have the following characteristics: They have a protective envelop to defend them against injury; they can live a

parasitic life; they grow and multiply; they are retained within the cytoplasm of the phagocytic cell; they destroy the cell; they escape, become extracellular and are phagocytosed again, and the cells containing them move from situation to situation. Within five hours, aggregations of phagocytic cells could be found filling the lumens of small bronchioles, and crowding together within alveolar sacs. They were potential tubercles. These aggregations appeared in that tissue, rich in lymphatic structures, which surrounds bronchi and vessels. The cells composing such aggregations appeared more actively phagocytic than those in adjacent interstitial tissue farther removed from a supply of oxygen. Such potential tubercles did not appear within the lymph follicles peripheral to large bronchi unless the bacilli had been introduced intravenously.

Within twenty-four hours the degree of pneumonic consolidation increased, and definite evidence of degeneration and fragmentation of polymorphonuclear cells appeared. Mononuclear cells became more and more numerous, and the large vacuolated phagocytes actively ingested not only large numbers of bacilli but also nuclear fragments or even whole polymorphonuclear cells. Along with evidence of necrosis, fat droplets were becoming conspicuous in the vacuolated cells and in those that were undergoing fragmentation. Mitotic figures appeared and bore testimony to the hyperplasia of mononuclear elements of fixed tissue origin.

After two days, although the large number of polymorphonuclear cells indicated that an exudative inflammation still existed, within the affected parts lesions appeared which were more discrete, more definitely spherical, peribronchial and increasingly mononuclear in type. Mitosis of nuclei, fat droplets in the cytoplasm of phagocytic cells and necrosis were much more conspicuous. When necrosis was most noticeable, and in those places in which the alveolar spaces were crowded with actively functioning mononuclear phagocytes, cells resembling fibroblasts enveloped spherical collections and produced the appearance of miliary tubercles set down in hyperplastic mononuclear pneumonic tissue. The central cells of the aggregation were mononuclear phagocytes, and an occasional degenerating polymorphonuclear cell was seen. There was a tendency to a central axial and a peripheral concentric arrangement of cells within the envelop of fibrils. Indistinct laminae were observable, the cells composing their layers being connected by the interlacing of their protoplasmic projections.

Within a week, the mononuclear cells had taken on the appearance and staining characteristics of mature epithelioid cells. Developing from simple inflammation characterized by a preponderance of polymorphonuclear cells, there had evolved a more specific inflammation characterized by a preponderance of mononuclear cells which were

recognizable as the epithelioid cell of the histologic tubercle of tuberculosis. The arrangement of cells in roughly spherical groupings with concentric laminae, their peripheral investment by fibroblasts and the enveloping zone of mononuclear cells of the lymphocytic order were characteristically and unmistakably those of tuberculosis. The forma-



Fig. 1.—*A*, massive and discrete lesions of experimental tuberculosis. The size of the lesion corresponds to the size of the bronchus to which it is adjacent. The subpleural lesions are small and discrete. *B*, lesions of experimental silicosis. The size, situation and physical characteristics of the lesions produce a close resemblance to lesions of tuberculosis. The lesions of tuberculosis and of silicosis are found in tissue rich in lymphatics and result from the cellular reactions induced by impounded *Mycobacterium tuberculosis* and particles of silica respectively.

tion of the tubercle occurred in association with the development of interstitial pneumonia. The tubercle might be isolated, but it was

usually seen as a discrete unit incorporated within a massive process of mononuclear pneumonitis. Within two weeks, however, gross evidence of the formation of tubercles occurred as isolated miliary tubercles distant from the massive tuberculous pneumonia that included all the structures of the lung adjacent to the large bronchi. The miliary tubercles were more adequately invested by fibroblasts, collagen appeared, and argyrophyl fibers penetrated into the center of the nodules, forming a fine interlacing meshwork. At this time, phenomena of obliteration appeared, and with them central necrosis could be observed. Caseation, excavation and ulceration developed, and in one

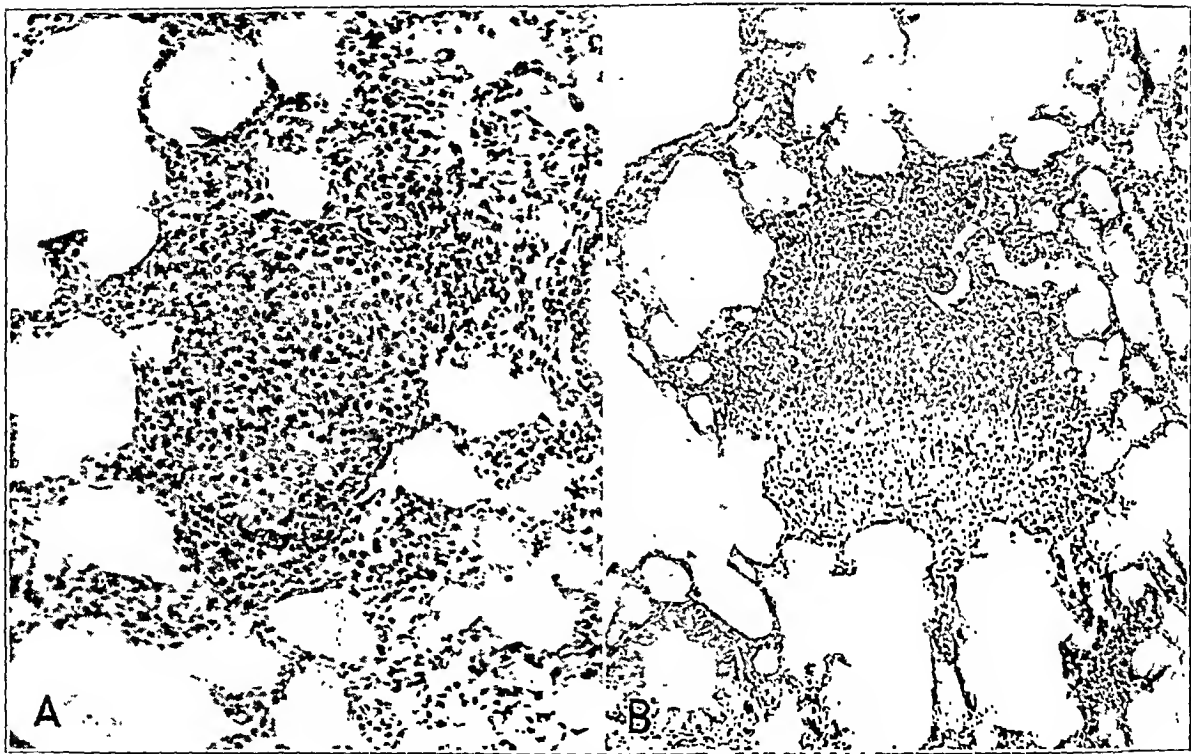


Fig. 2.—*A*, young, discrete peribronchial cellular tubercle of tuberculosis. *B*, young, discrete peribronchial cellular nodule of silicosis.

instance rupture of a tubercle into the lumen of its adjacent bronchus had already taken place. Within four weeks, caseous massive pneumonia created a central core of consolidation extending along the course of the bronchi, diminishing in size from hilus to periphery. Its physical characteristics of size and situation were determined by the anatomic distribution of lymphatic structures. It included within itself many discrete, encapsulated tubercles, many evidences of caseation and many of ulceration. About the periphery were numerous miliary tubercles of classic conformation. Giant cells had made their appearance, collagenous envelopes were more conspicuous, fibroblasts

and lymphocytes were included in the spaces between interlacing fibrils, wisps of collagen penetrated into the central portion of the tubercle, and a closely woven network of argyrophil fibrils composed the reticulum of the nodule.

In the lungs of animals which received an intravenous injection of virulent bacilli of tuberculosis of avian type, the miliary tubercles developed without obvious exudative inflammation. The earliest tubercles observed were minute spherical aggregations of mononuclear

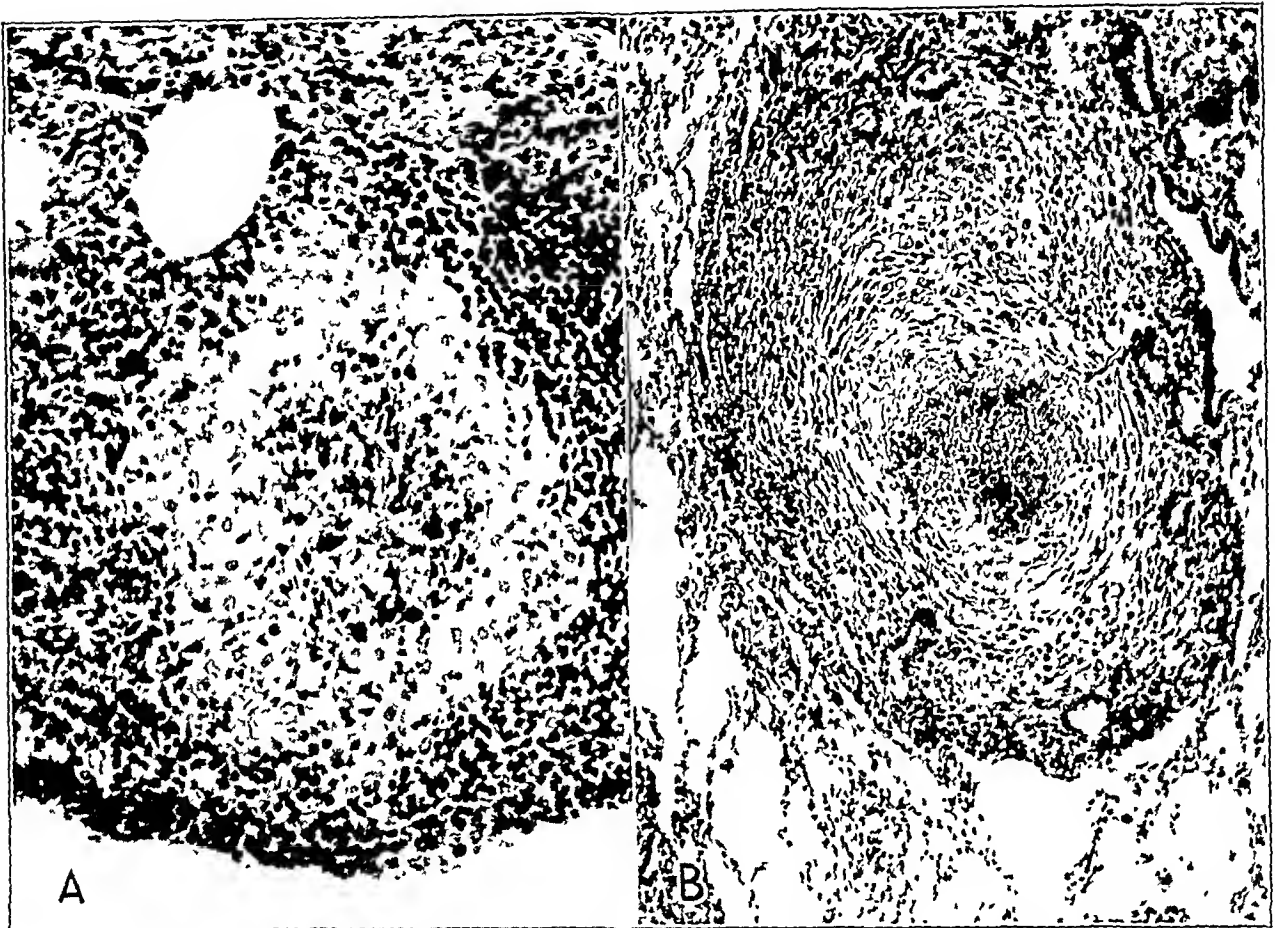


Fig. 3.—*A*, mature tubercle which developed three weeks following intratracheal inoculation of *Mycobacterium tuberculosis*, showing a central area of necrosis surrounded by indistinct layers of epithelioid cells and a peripheral wall of lymphocytes. *B*, silicotic nodule which developed three weeks following an intratracheal injection of silica. It has a similar central necrotic area, but the mononuclear phagocytic cells are more definitely arranged in concentric laminae. The formation of fibrous tissue is advancing about the periphery, and there is a narrow band of lymphocytes encircling the nodule.

cells recognizable as the typical epithelioid cells of the tubercle, surrounded by small mononuclear cells of lymphocytic type. Later, when infection had spread from the original foci, the tubercles became situated in lymphatic tissues approximating the bronchi and vessels, after

which the lesions passed through the same physical and cellular changes as those formed following intratracheal introduction of organisms. Obviously, the limited numbers of organisms introduced by way of the blood created an inconspicuous inflammatory response. The proliferative reactions with the creation of tubercle seemed to have appeared without any preceding exudative phenomena.

The Silicotic Nodule.—After the introduction of particulate silica into the lung, the inflammatory reactions are immediate, acute and

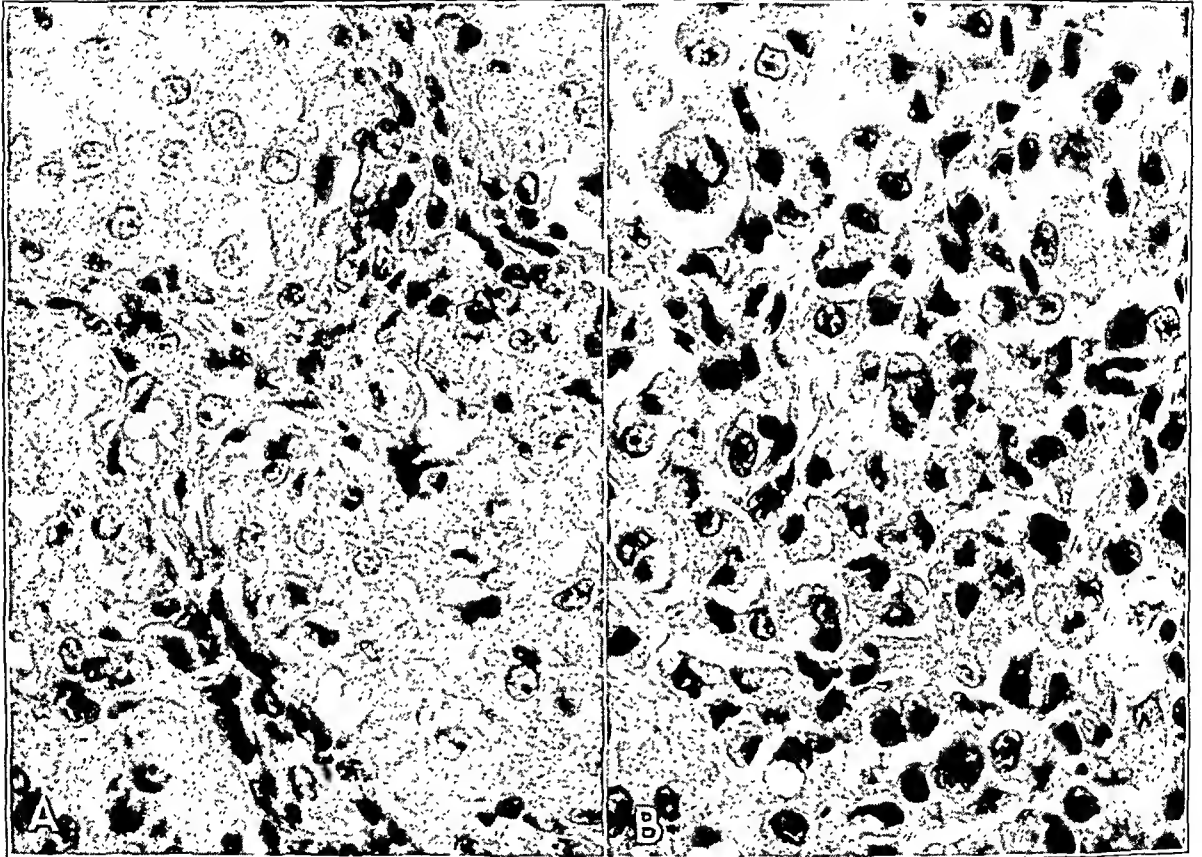


Fig. 4.—*A*, mononuclear phagocytic cells (epithelioid cells) from the mature tubercle of tuberculosis. Giant cells and mitotic figures are not seen in the illustration. *B*, mononuclear phagocytic cells (histiocytes) from the mature nodule of silicosis. Giant cells were never observed. Mitotic figures were occasionally found.

extensive. The pneumonitis is characterized by the exudation of a large amount of serum, an inrush of multitudes of polymorphonuclear cells and the formation of massive consolidation, largest at the hilus and ending as small focal peribronchial or peribronchiolar consolidations. The process of early phagocytosis by mononuclear cells started promptly, but was inconspicuous because of the preponderating inflammatory reactions.

The removal of the silica by both bronchial and lymphatic routes was promptly begun and rapidly accomplished. Many animals had completely rid themselves of silica within from four to eight hours. Many others were free from lesions a month after the injection. Silica must be arrested within the lung and must become fixed there before lesions can develop. Within three days, recognizable spherical aggregations of mononuclear phagocytes could be found. These were incorporated within the massive consolidations, or were discrete and situated mainly in tissue approximating the bronchi or the subdivisions of bronchi. By aid of the polarizing microscope, the particles of silica could be identified. They were found only where hyperplasia occurred and only where mononuclear phagocytes could be identified. In only a single instance was phagocytosis of silica observed in a polymorphonuclear cell. After three days the region of exudative pneumonitis decreased; the serum and erythrocytes disappeared from the parenchyma, and the polymorphonuclear cells became fragmented and decreased in number. There seemed to be a distinct stimulation of monocytes, the number of which rapidly increased.

Within a week monocytes were the most conspicuous cells in the massive consolidation, and the discrete lesions were composed of cells so arranged and so similar morphologically to epithelioid cells as to make the nodule indistinguishable from the young tubercle caused by the bacillus of tuberculosis.

During the second week a central necrotic zone developed in the nodule. This zone contained both free and phagocytosed particles of silica, peripheral concentric layers of mononuclear phagocytes containing phagocytosed particles, and an outer zone rich in fibroblasts lying in the meshwork of interlacing collagenous fibers. About the whole irregularly spherical nodule was a zone of lymphocytes which demarcated the nodule from the adjacent normal parenchyma. Fibroblasts and collagen passed from the periphery into the nodule, and a dense reticulum was demonstrable by differential staining methods. The transition of the mononuclear phagocyte into a cell similar to—if not identical with—the fibroblast could be observed in the outer layers of the mononuclear laminations. Fat droplets were conspicuous in properly stained sections; they were most conspicuous in the necrotic center but were also seen in the cytoplasm of the phagocytic monocytes. Ulceration into the bronchial or vascular structures did not occur within four weeks, but in the animals observed for two months it occurred not infrequently and was the cause of death of many animals. In one animal only was there replacement of the necrotic center by calcium salts. This animal was examined three weeks after receiving the injection. By the fourth week, there were increasing fibrosis, a heavier investment of the nodule by collagenous fibers, deeper penetration of

the nodule by collagen and a meshwork of dense and coarse argyrophil fibers within the nodule.

COMMENT

When the organisms of tuberculosis are introduced intratracheally into some animals, and when particles of silica are similarly introduced into others, the reactions leading to production of the specific nodules in both groups are the result of certain factors which the injected substances have in common. Each substance is relatively inert and relatively impervious to injury or destruction by the tissues; each has the ability to become arrested within the lung and thereafter to stimulate hyperplasia of mononuclear cells. In each instance, the lesion is found in regions rich in lymphatic tissue. The resulting specific lesion in each case is preceded by an exudative inflammation, more intense in the case of silica than in that of the organism of tuberculosis.

The ability of the living bacillus to grow and increase in number causes a provocative response which is progressive. The inability of silica to increase in number of particles and the progressive removal of the initial dosage cause a gradual decrease in the number and size of the lesions.

Phagocytosis of bacilli of tuberculosis by polymorphonuclear cells is much more frequent than phagocytosis of particles of silica. The most actively phagocytic cell in either case is the alveolar phagocyte. Both irritants stimulate hyperplasia of mononuclear cells which ultimately assume an epithelioid appearance, and the nodules formed are constructed of cells of this type. No significant differences could be discovered between the epithelioid cell of the tubercle and the mononuclear phagocyte of the silicotic nodule.

The tuberculous nodule retained its cellular integrity longer than the silicotic nodule; it developed a necrotic center more slowly and much more slowly became invested by collagen. The reticulum of the tuberculous nodule was slower in development and was composed of finer interlacing fibers. The tendency to the development of caseous, massive pneumonia and to a spread by ulceration into adjoining bronchi or blood vessels was much more evident in tuberculosis than in silicosis.

Both types of nodules were avascular and similarly constructed; they had a similar distribution of fat droplets and a similar distribution of bacilli or particles within the nodules.

Both lesions appeared to be the reaction of the reticulo-endothelial system to irritative substances capable of initiating comparable inflammatory phenomena.

SUMMARY AND CONCLUSIONS

In order to obtain material for a comparative study of the respective morphologic reactions provoked in the lung by particulate silica and by bacilli of tuberculosis, intratracheal injections were given to two series

of rabbits. The animals were killed at intervals of from four hours to four weeks after receiving the respective inoculums, and the course and character of the resultant cellular response were studied histologically. The results obtained appear to warrant the following conclusions:

1. The character of the cellular response to the irritative influences of particulate silica and to bacilli of tuberculosis is essentially the same; both promote the formation of characteristic tubercles.

2. The properties of the provocative agent responsible for the production of the silicotic tubercle preclude the formation of a structure characterized by continuous progression. This contrasts markedly with that formed as a consequence of the injection of bacilli of tuberculosis, which is usually of a progressive, destructive nature.

3. The similarity of the structural unit or tubercle invoked experimentally in response to particles of silica and to bacilli of tuberculosis is so striking as to make their certain differential identification impossible by ordinary morphologic criteria.

4. Although the pathologic characteristics of the two processes are practically identical during the early period of cellular progression, significant structural differences become evident as the duration of the diseases is extended.

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LIPOIDS AND LIPOID DISEASES

II. XANTHOMATOSIS (SCHÜLLER-CHRISTIAN'S TYPE)

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The clinical syndrome known variously as Schüller-Christian's disease, Christian's syndrome, xanthomatosis of the skeletal type and dysostosis hypophysaria and also described as "defects in membranous bones, exophthalmos and diabetes insipidus" was first described by Hand¹ in 1893. Hand presented the case of a 3 year old boy with exophthalmos and polyuria in whom autopsy revealed a soft, movable yellow spot about the size of a five cent piece, involving the entire thickness of the skull in the right parietal region. In 1916, Schüller² reported two cases, one in a boy of 16 with dystrophia adiposogenitalis, exophthalmos and marked cranial defects and the other in a girl of 4 years with polyuria, exophthalmos and defects of the skull. Schüller felt that both cases were examples of skeletal defects secondary to disease of the hypophysis. Christian,³ in 1919, reported a case of defects in the membranous bones, exophthalmos and diabetes insipidus, called attention to Schüller's case and, like Schüller, maintained that the syndrome was due to a pituitary disturbance. During the ensuing several years other examples of this syndrome were presented. Of particular interest is the report of Thompson, Keegan and Dunn⁴ of a case with complete postmortem examination. They concluded that the disease was not a pituitary dysfunction but was due to infection and that the symptom of polyuria, in accordance with the work of Bailey and Bremer⁵ and Curtis,⁶ was due to involvement of the hypothalamic region,

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Read before the Columbus Academy of Medicine, Columbus, Ohio, Nov. 7, 1932.

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in this case by pressure changes secondary to the cranial defects. Denzer,⁷ in 1926, pointed out that in view of the chronological development of the syndrome in his case, the bone defects are primary and exophthalmos and diabetes insipidus are incidental and not essential lesions.

The most important contribution to the problem of Schüller-Christian's disease was made by Rowland⁸ in 1928. He reviewed the literature, presented two cases of his own and showed that Schüller-Christian's disease is a special form of xanthomatosis, probably due to a primary disturbance of lipid metabolism closely related to essential xanthomatosis, Niemann-Pick's disease and Gaucher's disease. Epstein and Lorenz⁹ showed that there is a tendency to a specificity of lipid deposition in this group of conditions, the preponderant lipid varying with the disease. In Schüller-Christian's disease the lesions contain considerable cholesterol. In Niemann-Pick's disease phosphatides predominate, and in the lesions of Gaucher's disease cerebrosides are in the ascendancy.

The etiology of Schüller-Christian's disease is unknown. The relationship of the condition to diabetes insipidus and the constitutional evidence of pituitary dysfunction suggest a possible endocrine dyscrasia. However, these factors are probably secondary to defects in the skull; it is unlikely that endocrine dysfunction is of etiologic importance. Infection has been shown to have a chronological connection with the disease, but as is true of the majority of childhood diseases, it is nearly always possible to obtain a history of a preceding infection. Trauma seems to play a part in the etiology, since a history of trauma at the site of defects in the skull previous to their development is common, and it is true that in essential xanthomatosis the cutaneous lesions develop at points subjected to the most trauma. There is phagocytosis of lipoids by the cells of the reticulo-endothelial system. Whether this is due to an avidity of the cells for lipoids or is a compensatory mechanism resulting from a failure of proper fat metabolism is problematic. Rowland expressed the belief that there is a constitutional anomaly of lipid metabolism, and that this constitutional tendency plus various external factors may produce the disease.

Pathologically, Schüller-Christian's disease is characterized by yellowish, rubbery lesions arising from the dura, extending for varying distances through the tables of the skull and eventually occupying its

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entire thickness. In the long bones, similar lesions are found extending inward from the periosteum. Scattered throughout the bone marrow and viscera are small yellowish areas of the same quality, microscopically, as the bone lesions. Histologically, these lesions consist, early in their development, of a mass of lipoid-laden histiocytes known as xanthoma or foam cells. As the process grows older there is connective tissue proliferation with fibrotic replacement of the xanthoma cells. This fibrotic element reaches the clinical horizon most notably in the lungs, since pulmonary fibrosis is marked and is commonly the cause of death in this condition.

The onset of the disease is insidious. The patient is most often brought to the physician complaining of exophthalmos, excessive thirst and polyuria, failure to gain weight, irritability, tenderness on handling and sore mouth. The disease progresses slowly, and there are apparent quiescent intervals of varying length. As the disease continues, dyspnea and cyanosis develop owing to the pulmonary fibrosis, the primary symptoms become more marked, pathologic fractures may occur, the teeth become loosened and anemia develops as a result of the marked bone marrow displacement. Examination of the patient reveals punched-out areas of bone destruction and tenderness over the skull and the long bones. The spleen and liver are palpable but not markedly enlarged.

The blood is normal or shows mild secondary anemia early in the disease. With considerable involvement of the bone marrow an aplastic type of anemia may develop. There is no typical blood picture, and the xanthoma cell has not been found in the circulating blood.

Rowland stated that the cholesterol, lecithin and fatty acids of the blood are increased during the active stage but during the periods of apparent quiescence are normal. In other respects the blood chemistry has been found to be normal.

Routine laboratory tests give negative results. Roentgen examination shows multiple punched-out areas of bone displacement involving the membranous bones and often the long bones as well.

REPORT OF A CASE

Dorothy G., a 21 month old girl, was admitted to the University of Michigan Hospital in March, 1932, with a chief complaint of "anemia." Her birth was instrumental but uneventful; her development was normal, and the past history was entirely unimportant. The patient's mother was 21 years old, of French descent and healthy; the father was 24 years old, likewise of French descent and healthy. There was no family history referable to the xanthomatoses.

The present illness began at the age of 15 months, six months prior to admission, with the spontaneous appearance of a tumescence on the inferior border of the right mandible. This swelling appeared benign. There was no associated redness or heat, although there was some tenderness to palpation. The child had no coincident infection of the mouth or the upper respiratory tract, and the process

was unattended by fever. At this time the child fell and suffered a trauma to the left parietal region. A firm tumor which showed no tendency to involute developed at the site of the trauma. The child failed to gain weight and was restless and irritable. Three months after the onset of the illness the mandibular swelling disappeared, and coincident with its disappearance there was a small amount of foul-smelling, yellowish discharge from the right ear. Some swelling developed over the right mastoid area, and in the fourth month of the illness mastoidectomy



Fig. 1.—The patient on admission to the hospital.

was performed on the right side. The otologist found no pus at the time of operation but observed a small amount of yellowish granulation tissue. Shortly after the operation a pathologic fracture of the right femur developed, and the mother discovered a soft spot in the skull in the left parietal region at the site of the posttraumatic tumor. During the two months previous to admission progressive and marked anemia developed which necessitated repeated transfusions.

On admission the infant exhibited marked pallor. There was slight dyspnea. The pulse was rapid and thready. Over the scalp and in the midline of the chest

and of the back was a papulosquamous eruption covered with yellow, oily scales, confluent on the scalp and fairly discrete on the trunk. There was no excoriation indicative of pruritus over the involved skin. There was moderate edema of the ankles. Examination of the skull showed a mastoidectomy wound on the right with little evidence of healing. In the right parietal region there was a soft, punched-out area of bone destruction about 1 inch (2.5 cm.) in diameter. The lower right molars were loose, and the gums were spongy and injected. The tonsils were hypertrophic and septic. The lungs were normal. The heart was slightly enlarged; the rate was rapid; the sounds were of poor quality, and there was a soft blowing systolic murmur at the apex. The spleen was felt 1 inch below the left costal margin, and the edge of the liver was felt about 2 inches (5 cm.) below the right costal margin. There was genu valgum of the right leg, and pain and tenderness were noted on manipulation of the extremities. There was no remarkable lymphadenopathy. The urine was normal. The hemoglobin was 15 per cent (Sahli), and the erythrocyte count, 900,000. The leukocyte count was 7,000, and the smear showed 47 per cent neutrophils, 49 per cent lymphocytes and 4 per cent monocytes. The platelets were definitely decreased. The red

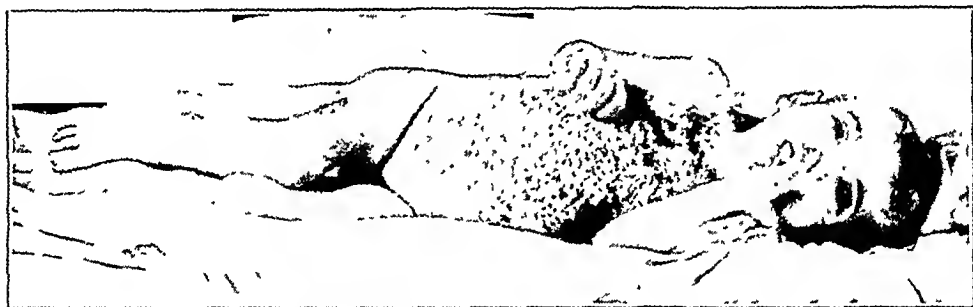


Fig. 2.—The patient a few days before death.

cells showed moderate achromia. Occasional stippled cells and nucleated red cells were found.

There was no gross lipemia. The blood cholesterol was 182 mg. per hundred cubic centimeters; phosphorus, 2.8 mg. and calcium, 9.4 mg. The serum protein was 5.2 Gm. per hundred cubic centimeters.

The tuberculin and the Kahn test of the blood were negative.

Roentgen examination of the skeletal system demonstrated multiple lesions of the skull, the right mandible, both scapulae, the left humerus and both lower extremities. These lesions were well defined areas of apparent complete decalcification.

Bone marrow smears were obtained by biopsy, and xanthoma cells were found.

The course of the disease while under my observation was essentially that of aplastic anemia. The anemia progressed, blood platelets became practically absent and the white blood cell count dropped to as low as 2,600, with 20 per cent neutrophils. There were marked purpura, frequent epistaxis and bleeding from the gums. Several transfusions were given with but transitory relief. The patient became more dyspneic than even the progressive anemia warranted, and during her last week in the hospital the oxygen tent was necessary. Owing to exsanguination, generalized anasarca gradually developed, and the child died on the fortieth day in the hospital.

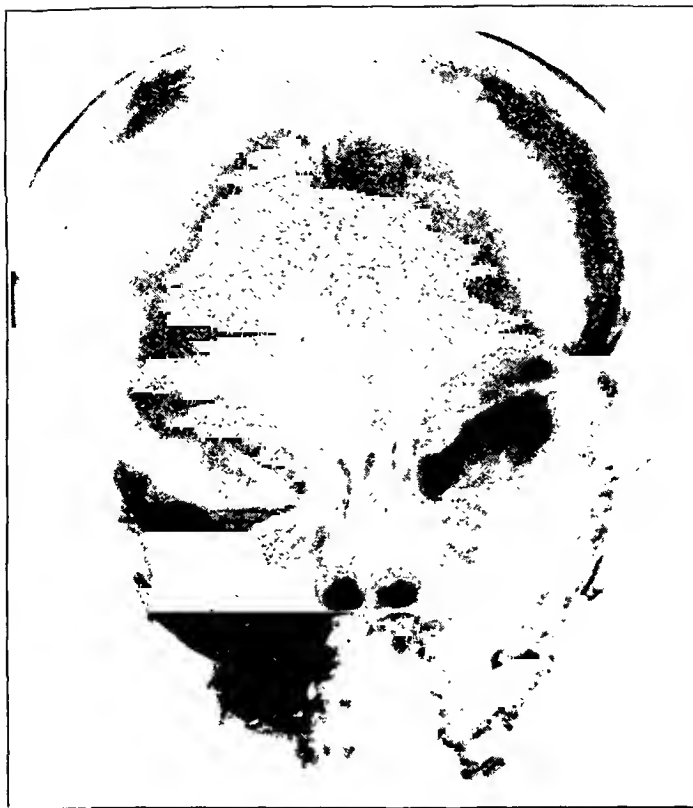


Fig. 3.—Anteroposterior roentgenogram of the skull showing multiple lesions of the calvarium and involvement of both mandibles, particularly the right.



Fig. 4.—Lateral view of the skull. The large temporal lesion was found on physical examination.

The results of pathologic examination, conducted by Dr. C. V. Weller, were as follows: The skull cap showed a soft, discolored area about an inch in diameter in the left parietal region. Several small yellow areas were observed in the inner table. There was a patchy thickening of the dura with small yellowish deposits on its inner surface. These areas of thickening were microscopically made up of young fibroblasts, reticulo-endothelial cells, small multinucleate giant cells and foam cells. There were similar deposits with dense adhesions along the periosteal surface. The hypophysis was essentially normal, but the sella turcica

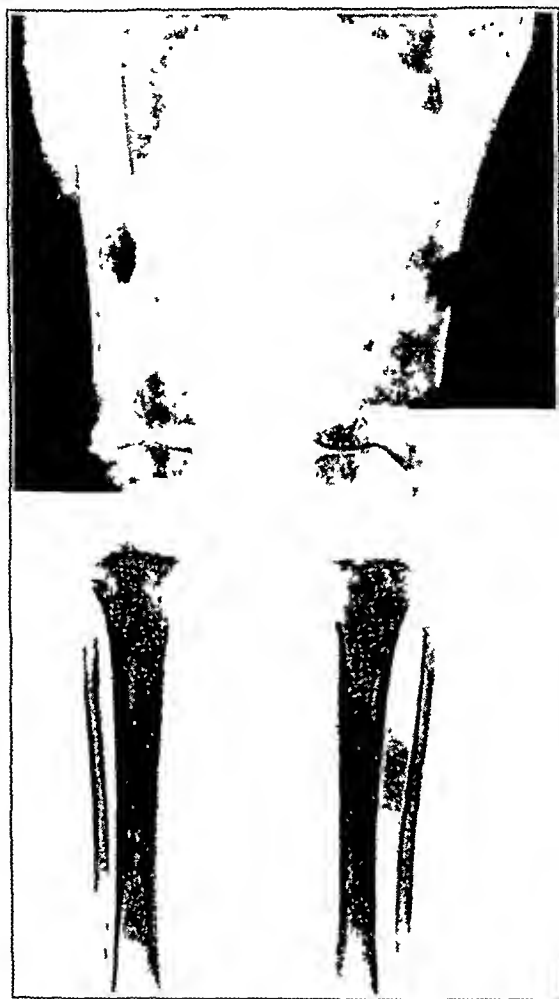


Fig. 5.—Defects in both femurs with pathologic fracture and consequent genu valgum.

was almost entirely replaced by the yellowish xanthomatous material. The wings of the sphenoid and the temporosphenoid area were likewise markedly infiltrated by the same substance. There was no xanthomatous involvement of either orbit.

In the costovertebral gutter on the right was a yellow tumor the size of a half dollar involving the ninth rib. There was a similar area the size of a dime on the seventh rib on the left side. Examination of the heart disclosed a small yellowish mass on the anterior surface of the right auricle and a few minute yellowish areas at the base of the aortic valve, and on microscopic examination granulation tissue containing typical foam cells was found in the auriculoventricular sulcus.

The lungs were doughy. At the base of the left lung a small xanthoma was found. Microscopic examination of the lungs showed diffuse fibrosis, obliterating to various degrees most of the smaller bronchi (fig 9). Some of the pulmonary



Fig. 6—Anteroposterior view of the chest, showing lesions of both scapulae and marked increase of the hilar shadows due to xanthomatous infiltration and fibrosis



Fig. 7.—Postmortem roentgenogram of the calvarium.

arteries showed calcification, and fat stains demonstrated lipoid-containing cells free in the alveolar spaces and present in small numbers about the vessels and bronchi (figs 10 and 11).

The spleen was enlarged and microscopically showed marked congestion and localized areas of fibrosis containing foam cells and phagocytes loaded with brownish pigment. The liver was slightly smaller than normal, and fat stains showed no evidence of lipoidosis. Xanthomatous lesions were also found in the suprarenal cortex, the renal pelves and the long bones. In addition to the xanthomatous lesions there were marked calcification of the arteries, atrophy and parenchymatous degeneration of all organs, bilateral hydrothorax and ascites.

The clinical picture in this case of xanthomatosis differed from the usual one in several respects. Although there was considerable xantho-

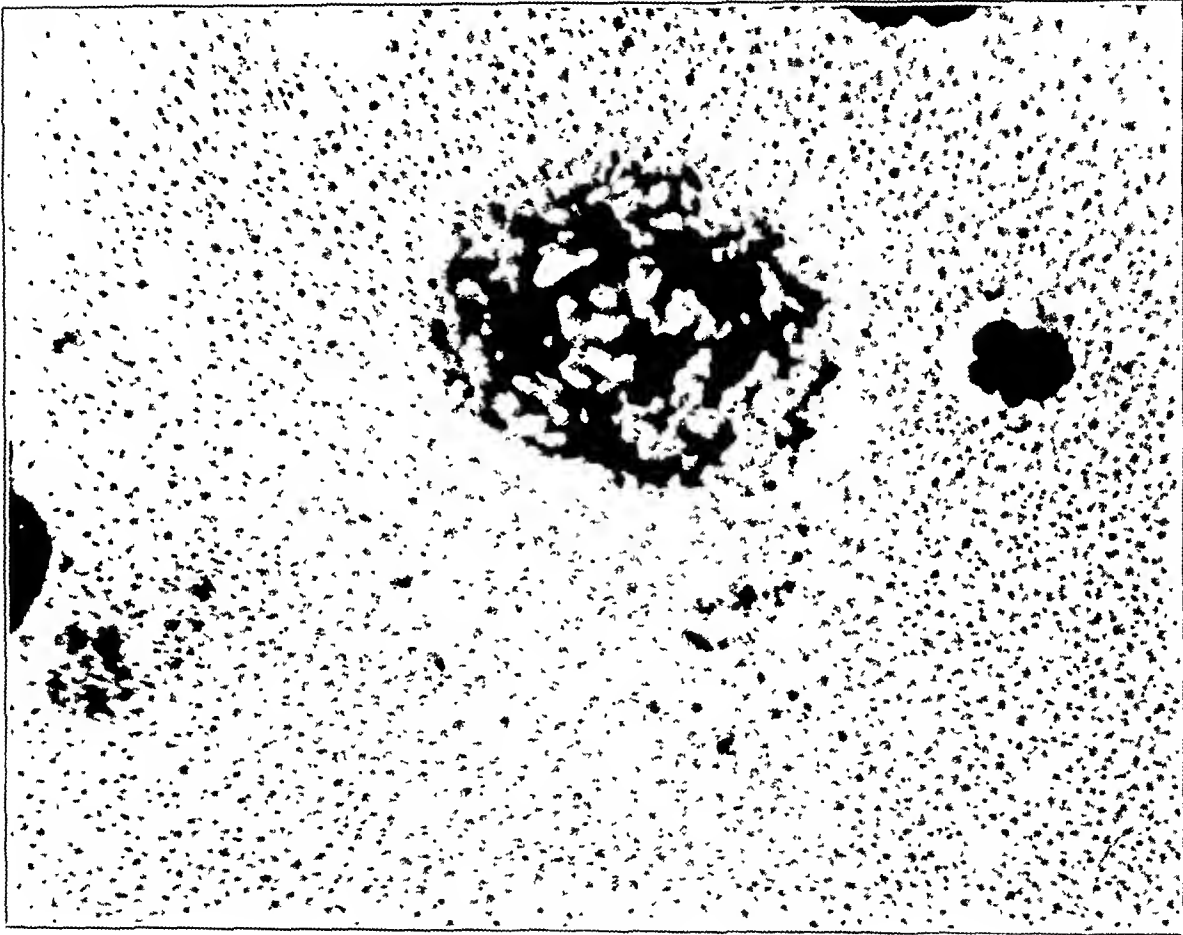


Fig. 8.—Foam cell (bone marrow).

matous infiltration at the base of the skull, particularly in the sella turcica, the pathologic changes in that region were apparently not great enough, or not of the proper form, to cause a reaction in the hypothalamic region sufficient to lead to the production of diabetes insipidus. However, had the patient lived longer, it is not unlikely that polyuria and polydipsia would eventually have developed. There was no pathologic evidence of xanthomatous involvement of the bony orbit, which adequately explains the absence of exophthalmos. The osseous lesions, both roentgenologically and pathologically, were characteristic of Schüller-Christian's disease. Although pathologic fracture is common

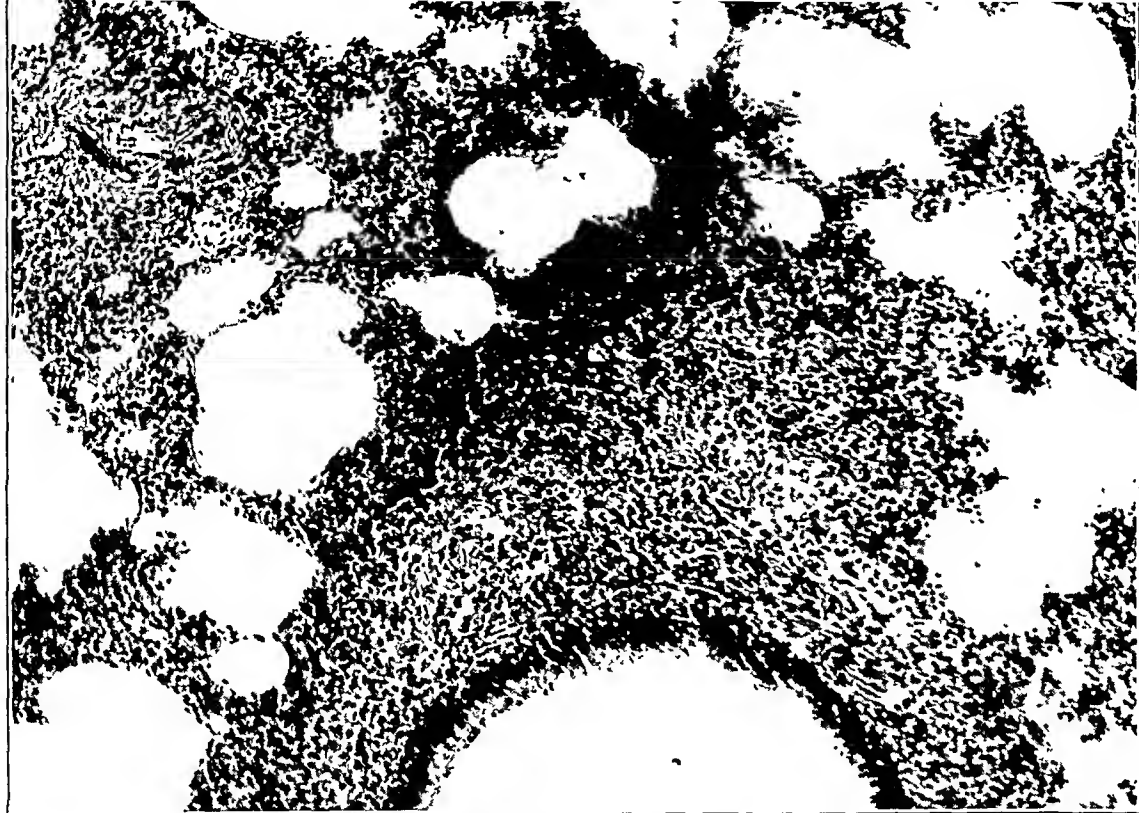


Fig. 9.—Pulmonary xanthomatosis and fibrosis.

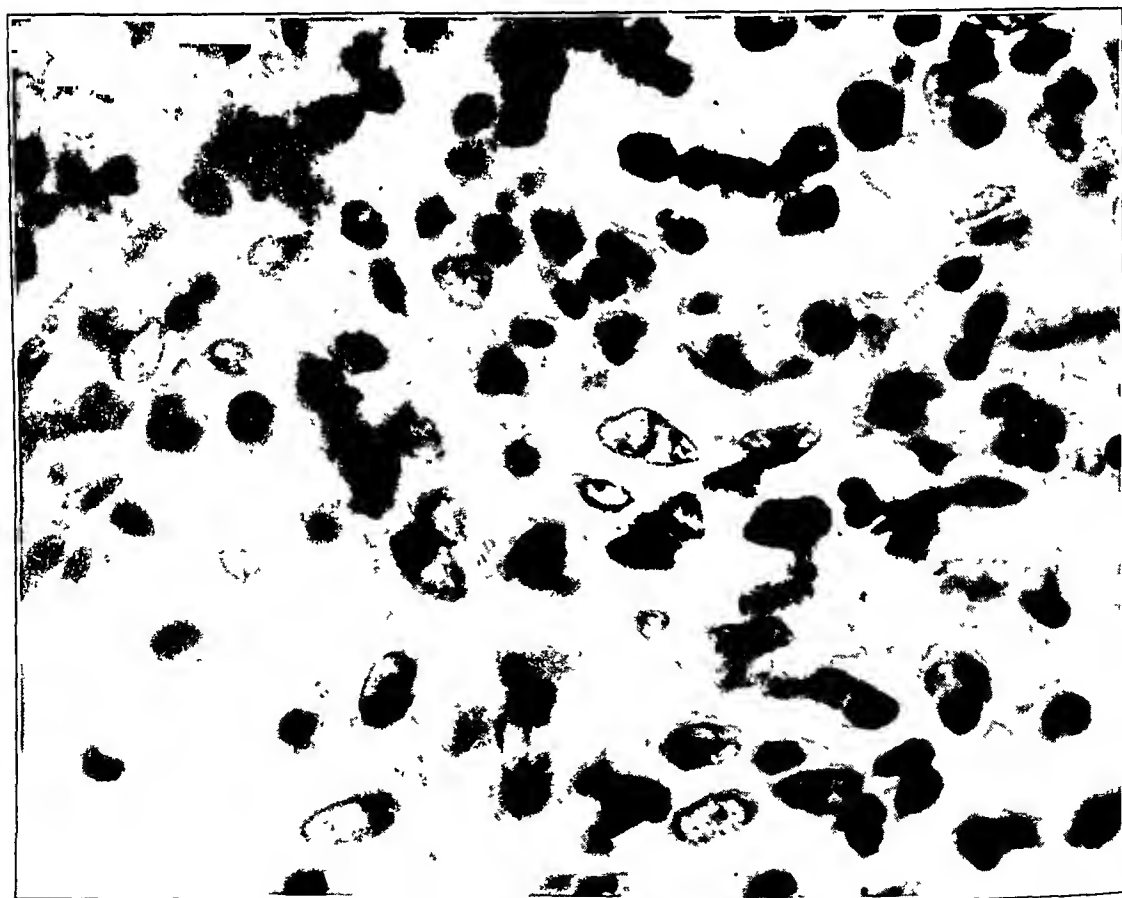


Fig. 10.—High power view of figure 9, showing foam cells and fibroblasts.

in Gaucher's disease, this case presents the first recorded instance of spontaneous fracture in the Schüller-Christian type of xanthomatosis.

The fact that xanthomatous infiltration of the temporal bone may simulate mastoiditis is well demonstrated in this case. A discharging ear developed, with postauricular tenderness and swelling. It is probable that had preoperative roentgen examination been made there would have been adequate roentgenologic evidence to rule out acute suppurative mastoiditis. That the operation was harmful in this case cannot be



Fig. 11.—Osmic acid stain of a section of the lung, demonstrating the presence of considerable lipid substance.

said with certainty, but it happened at a critical point in the illness, and the course after operation was rapidly downhill.

The severe aplastic anemia is commonly a part of the terminal stage of the disease, and reasonably so in view of the marked xanthomatous infiltration of the bone marrow. The marked hemorrhagic tendency was likewise a manifestation of inactivity of the marrow. Hemorrhagic phenomena are, however, more common in the terminal stages of the Gaucher's type of xanthomatosis than in Schüller-Christian's disease.

Cutaneous lesions have been described in a number of cases of the Schüller-Christian type of xanthomatosis. Rowland mentioned the pigmentation that may occur as a result of accumulation of lipochrome

pigments and stated that when present the eruption is primarily composed of pink papules which grow in size and become xanthomas. Microscopically these cutaneous lesions contain lipid-laden foam cells. The eruption in this case was a typical seborrheic dermatitis, and no evidence of xanthomatous infiltration of the skin was found on microscopic examination.

There was no gross lipemia or cholesteremia in this case suggestive of faulty fat metabolism. Chemical examination of the blood showed a low normal calcium and a low phosphorus content although there was no evidence of rickets and the infant had received a balanced diet with adequate vitamin D previous to her illness. The marked arteriosclerosis was likewise interesting; it may be explained perhaps by the arterial deposition of calcium displaced by xanthomas from the bones by a mechanism similar to that occurring with huge doses of vitamin D.

The influence of diet on Schüller-Christian's disease is problematic. Rowland observed beneficial effects in one case in which the patient was on a low fat diet. His result is difficult to evaluate since patients with this disease at times have spontaneous remissions and Rowland administered pituitary and thyroid with the low fat diet. Wile, Eckstein and Curtis found in studying xanthomatosis of the skin that while a low fat diet has a beneficial effect in diabetic cases in which the lesions seem directly related to the lipemia there is no demonstrable relationship between blood fat and the lesions of essential xanthomatosis, and the amount of fat in the diet has no bearing on the course of the disease. Since there is close similarity between the Schüller-Christian and the essential type of xanthomatosis, particularly in that the clinical progress does not depend on the presence or degree of lipemia, in either type it seems logical that a low fat diet is probably of little therapeutic value.

Roentgen irradiation has been tried in a number of cases. Sossman reported good results, particularly in the tendency to involution of the osseous lesions under therapy. The difficulty, particularly in the case reported here, in which there was profound aplastic anemia, was in irradiating the lesions without producing further depression of the bone marrow.

LIPOIDS AND LIPOID DISEASES

III. LIPOID CONTENT OF TISSUES IN SCHÜLLER-CHRISTIAN'S DISEASE (XANTHOMATOSIS) AND REVIEW OF LITERATURE ON LIPOID CONTENT OF HUMAN TISSUES

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We present here a study of the lipoid content of the various tissues of the body in a case of Schüller-Christian's disease together with a review and discussion of the literature to date. Because of the severe anemia encountered in this case we include a parallel study on the tissue of a child of about the same age with similar anemia due to another cause. It was our idea that the latter might in a way act as a control. It has been our hope that should a case of accident come to autopsy we could present our own normal figures. This opportunity has not presented itself.

METHODS

The material was obtained from the autopsy table as soon as possible. All extraneous blood and tissue were carefully removed. None of the tissue was perfused. It was ground in a meat grinder and weighed. It was then placed in 95 per cent alcohol, the volume being at least three times that of the tissue. The air in the flasks was replaced by nitrogen. The tissue was allowed to remain in the alcohol for forty-eight hours. The alcohol was then decanted, fresh 95 per cent alcohol added and the mixture allowed to stand for forty-eight hours. Again the supernatant alcohol was decanted and absolute alcohol added. This was allowed to stand for three days, after which the alcohol was replaced by fresh absolute alcohol. The extraction with absolute alcohol was repeated, and the combined decantations were filtered. The tissue residue was rinsed with ether at least three times. It was then dried in a vacuum desiccator, after which it was ground finely in a coffee grinder. The ground residue was refluxed with absolute alcohol, two portions of alcohol being used. The material was refluxed for from thirty-six to seventy-two hours, depending on the amount of tissue examined. The tissue residue was again thoroughly rinsed with ether.

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Chloroform was used after the extraction in the first few analyses. The amount of lipid extracted by this means was negligible. This step in the procedure was subsequently discontinued. The combined alcohol and ether extracts from the hot and cold methods were concentrated in

TABLE 1.—*Lipoids in Various Tissues in Case 1*

Tissue	Pathologic Changes	Weight of Sample, Gm.	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospho-lipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospho-lipoid-Cholesterol Ratio
Liver	No lipoidosis; atrophy; increased stroma	150	3.17	2.24	0.398	6:1
Left lung	Diffuse fibrosis, mainly perivascular and peribronchial; phagocytes containing lipid in these areas and in alveoli	65	3.01	1.69	0.432	3.9:1
Spleen	Congestion; localized areas of fibrosis containing foam cells and phagocytes loaded with brown pigment	35	2.36	1.53	0.286	5.3:1
Kidneys (one half of each)	Cloudy swelling; calcification of renal vessels and calcium deposits in tubules (no lipoidosis)	40	2.40	1.33	0.250	5.3:1
Suprarenal gland (entire gland)	Atrophy; medulla proportionally abundant	1.4	7.07	1.25	2.08	1:1.7
Heart (ventricular wall)	Serous atrophy of subpericardial fat; subendocardial degenerative fatty infiltration	11	2.66	1.82	0.174	10.5:1
Psoas muscle	Very edematous; pale	13	0.90	0.47	0.128	3.7:1
Rectus muscle	Very edematous; pale	8	0.84	0.47	0.110	4.3:1
Bone marrow (distal end of femur, approximately normal)	Cellular, hyperplastic marrow in some areas; edematous fibrous connective tissue in others	7.3	3.01	1.04	0.664	1.6:1
Xanthoma from proximal end of femur	Yellow, tough and fibrous; no resemblance to normal bone marrow; similar to xanthoma in dura	4.4	7.39	1.59	4.023	1:2.6
Xanthomata (small masses from orbital, occipital and temporal regions; approximately 10% of weight is adherent dura and periosteum)	Localized areas of thickening containing young fibroblasts, reticulo-endothelial cells, small multinucleated giant cells and many foam cells	1	6.96	0.83	3.462	1:4.2

vacuo to a convenient volume. Adequate samples were then evaporated almost to dryness and redissolved in purified petroleum benzine (20°—40° redistilled). The solution was washed with water to remove any water-soluble material, such as pigments. It was then made up to a convenient volume, and samples were used for the determination of total lipid, cholesterol and phospholipoid.

For the determination of total lipid, an aliquot part of the solution was placed in a weighed dish, the ether evaporated and the weight of the residue determined. For the determination of lipid phosphorus, the Whitehorn¹ method was used. The phospholipoid content was estimated by multiplying the amount of lipid phosphorus by the factor 26. For the determination of cholesterol, Sackett's² method was used. Duplicate tests were made in all determinations.

REPORT OF CASES

CASE 1.—*D. G., aged 21 months. Schüller-Christian's disease.*

A complete clinical and pathologic report of this case was given in the preceding paper in this series by Lichty³ and will not be repeated here. The pathologic diagnosis was: Schüller-Christian's disease; localized cholesterol ester lipoidoses in the dura, skull cap, base of the skull, pituitary fossa, ribs, right femur, thymic area, lungs, subpericardial tissues, submucosa of the renal pelvis and skin and in many lymph nodes; bony defects in the skull cap, seventh and ninth ribs, mandible and right femur; patchy fibrosis of the lungs; marked calcification of the arteries; anemia; petechial hemorrhages in the skin, right lung and pericardium; atrophy and parenchymatous degeneration of all organs; bilateral hydrothorax; ascites. The results of the determinations of lipoids are recorded in table 1.

CASE 2.—*S. B., aged 10 months. Severe secondary anemia with delayed maturation of the red blood cells.*

The child was admitted to the clinic because of progressive loss of weight for two or three months and anorexia, regurgitation and diarrhea for two weeks before entrance.

On examination she was very irritable. The skin showed a peculiar yellowish color, but there was no definite icterus. There was evidence of loss of weight, but the panniculus was still thick, particularly over the lower extremities. The tone of the skin was gone, and the skin hung in folds filled with firm fat. The gums were tender, with some bleeding along the alveolar ridge. The glands, lungs, heart and abdomen were essentially normal. There was bilateral knee jerk clonus. The other reflexes were normal. Ophthalmoscopic examination showed that the disks in both eyes were slightly edematous and had a grayish-ashen hue. Roentgen examination of the long bones showed nothing abnormal. The urine was normal. The blood chemistry is recorded in tables 2 and 3. The patient was given one transfusion of 90 cc. of blood, which was followed by a rise in temperature. Soon after this signs of bronchopneumonia developed, and the child died on the tenth day in the hospital.

The pathologic diagnosis was: Anemia of undetermined origin resembling pernicious anemia; terminal bronchopneumonia; asphyxiative death; aspiration of food into the respiratory passages; petechial hemorrhages into the lungs and meninges; acute passive congestion of all organs; fatty infiltration of the liver; terminal cardiac dilatation; fibroid atrophy of the thymus. The results of the analysis of tissues are recorded in table 4.

1. Whitehorn, J. C.: J. Biol. Chem. **62**:133, 1924.

2. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.

3. Lichty, D. E.: Lipoids and Lipoid Diseases: I. Xanthomatosis (Schüller-Christian Type), Arch. Int. Med., this issue, p. 379.

TABLE 2.—*Findings in Blood*

	Schüller-Christian's Disease	Severe Secondary Anemia
Hemoglobin.....	45%	47-44%
Red cells.....	1,500,000	3,710,000-1,780,000
Color index.....	1.5	1.46
White cells.....	3,500	11,100-9,600
Reticulocytes.....	++	++
Polymorphonuclears.....	50%	64.2-48%
Large lymphocytes.....	20%	12.5%
Small lymphocytes.....	30%	16%
Total lymphocytes.....	50%	54-28.5%
Monocytes.....	9%	1%
Eosinophils.....	0%	1%
Anisocytosis.....	+	+
Poikilocytosis.....	+	+++
Stippled red cells.....	+	+
Nucleated red cells.....	+	+
Pencil forms.....	—	+
Myelocytes.....	±	0
Macrocytes.....	++	++
Microcytes.....	+	—
Achromia.....	0	+
Polychromatophilia.....	+	—
Platelets.....	±	+ normal

TABLE 3.—*Blood Chemistry*

	Schüller-Christian's Disease	Severe Secondary Anemia	Comment
Nonprotein nitrogen.....	23	40	Case of Schüller-Christian's disease showed calcification of renal vessels, calcified thrombus, lime salt deposit in some tubules and calcification of suprarenal arteries; no such changes in case of anemia
Sodium chloride.....	533	505	
Cholesterol.....	182-160	110	
Phospholipoid.....	...	112	
Total lipid.....	...	429	
Serum calcium.....	9.4	9.7	
Serum phosphorus.....	2.8	3.8	
Carbon dioxide-combining power.	39% by volume		
Serum protein.....	5.2 Gm.		
Serum albumin.....	2.7 Gm.		
Serum globulin.....	2.5 Gm.		
Blood group.....	II	IV	
Kahn test.....	0	0	

TABLE 4.—*Lipoids in Various Tissues in Case 2*

Tissue	Pathologic Changes	Weight of Sample, Gm.	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospholipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospholipoid-Cholesterol Ratio
Liver	Cloudy swelling; fatty infiltration	56.5	8.09	1.79	0.280	6.4:1
Lungs	In lower lobes, aspiration pneumonia and abundant fat droplets in bronchi and alveoli; upper lobes grossly showed very slight involvement; upper lobes used for analysis	17	4.62	1.33	0.335	4:1
Spleen	Congestion	8	3.64	1.43	0.337	4.3:1
Kidneys (one half of each)	Passive congestion; cloudy swelling	18.5	4.02	1.14	0.362	3.2:1
Heart (ventricular wall)	Hypoplasia of muscle.....	5.5	4.19	1.43	0.118	12.1:1
Rectus muscle	Congestion	9	5.9	0.49	0.121	4:1

COMMENT

The lipoids in the tissues in our case of Schüller-Christian's disease (table 1) showed no marked differences from those of normal persons, except in the xanthomatous masses. The results of analysis of these masses are in agreement with the figures recorded by Epstein and Lorenz⁴ and by Kleinman.⁵ The lipid content was high (from 6.96 to 10.37 Gm. per hundred grams of tissue). At least from 40 to 50 per cent of the total lipid was cholesterol. The cholesterol content of the xanthomata was much higher than that found in the various normal tissues. The phospholipoid content (from 0.45 to 0.83 Gm.) was much lower than that found in the other tissues of the body examined and than that found in normal tissue with the exception of voluntary muscle.

The proximal end of the right femur was the site of a xanthoma one-third the length of the femur (shown in the roentgenogram [fig. 5] in the preceding article³) which had practically replaced the marrow. At the distal end of the bone the marrow appeared more nearly normal. The total lipid content of the xanthoma (7.386 Gm. per hundred grams of tissue) was found to be twice that of the marrow at the distal end of the bone (3.013 Gm.). The cholesterol content of the xanthoma (4.023 Gm.) was six times as great. On the other hand, the phospholipoid content of the xanthoma (1.59 Gm.) was distinctly higher than that of the marrow of the distal end of the bone (1.047 Gm.). The total lipid and the cholesterol content of the xanthoma of the bone marrow were very similar to those of the dura. The phospholipoid of the xanthoma of the bone marrow was almost twice as great as that of the xanthoma from the dura. No explanation for this difference is at hand.

In table 5 will be found a review of the literature on the total lipid, phospholipoid and cholesterol content of human tissues. The analyses are so arranged as to be easily compared with the results that we have obtained in the two cases presented. We were unable to use the figures in several reports because the determination of the lipid content was on the basis of grams per hundred grams of dried tissue, and the percentage loss of water was not given. In some of the reports the water content was given. This enabled us to calculate the lipid content in terms of grams per hundred grams of wet tissue, this being the basis of our analysis.

By reference to table 5 it will be seen that Kleinman reported a high cholesterol content in the liver and spleen in his case of Schüller-Christian's disease, while we were unable to show an increase above

4. Epstein, E., and Lorenz: *Ztschr. f. physiol. Chem.* **192**:145, 1930.

5. Kleinman, H.: *Virchows Arch. f. path. Anat.* **282**:613, 1931.

TABLE 5.—*Lipoid Content of Human Tissues as Reported in the Literature*

Tissue	Age	Reporter	Pathologic Diagnosis	Total Lipoid, Gm. per 100 Gm. Fresh Tissue	Phospho- lipoid, Gm. per 100 Gm. Fresh Tissue	Cholesterol, Gm. per 100 Gm. Fresh Tissue	Phospho- lipoid- cholesterol Ratio
				3.34	0.285
Liver	8 mos. fetus	Beumer ⁷	4.44	0.341
	5½ yrs.	Beumer	Pulmonary and meningeal tuberculosis.....	2.85	0.180
	11 mos.	Beumer	von Jakseh's anemia	3.04	1.79
	22 yrs.	Theis: J. Biol. Chem. 82: 327, 1929.	Normal	3.45	1.71
	35 yrs.	Theis	Normal	5.16	1.71
	Died at birth	Theis	0.324
	20 yrs.	Fex: Biochem. Ztschr. 104: 82, 1920.	Normal	0.377
	29 yrs.	Fex	Normal	0.254
	30 yrs.	Fex	Normal
	10 mos.	Authors' ease	Secondary anemia (fatty degeneration of liver)	8.09	1.79	0.280	6.4:1
	2 yrs.	Authors' ease	Schüller-Christian's disease	3.17	2.24	0.398	6:1
	3 yrs.	Kleinman ⁵	Schüller-Christian's disease	4.46	0.291	1.060	1:3.6
Spleen	3 mos. fetus	Beumer ⁷	1.95	0.368
	8 mos. fetus	Beumer	1.83	0.306
	6 yrs.	Beumer	Polyarthritids; secondary anemia.....	3.284	0.235
	Infant	Kleinman ⁵	Normal	1.108	0.297	0.162	1.8:1
	10 mos.	Authors' ease	Secondary anemia	3.64	1.43	0.337	4.3:1
Lungs	3 yrs.	Kleinman ⁵	Schüller-Christian's disease	1.07	0.254	0.794	1:3.1
	2 yrs.	Authors' ease	Schüller-Christian's disease	2.36	1.53	0.286	5.3:1
	3 mos. fetus	Beumer ⁷	1.47	0.188
	8 mos. fetus	Beumer	1.30	0.166
	10 mos.	Authors' ease	Anemia; terminal bronchopneumonia.....	4.62	1.33	0.335	4:1
Kidneys	2 yrs.	Authors' ease	Schüller-Christian's disease	3.01	1.69	0.432	3.9:1
	Windaus: Ztschr. f. physiol. Chem. 65: 110, 1910	2.06	0.272
	8 mos. fetus	Windaus	Normal	1.87	0.250
	6 yrs.	Beumer	2.87	0.275
	11 mos.	Beumer	Polyarthritids; secondary anemia.....	4.25	0.134
	20 yrs.	Beumer	von Jakseh's anemia	3.17	0.199
	29 yrs.	Fex: Biochem. Ztschr. 101: 82, 1920.	Normal	0.310
	30 yrs.	Fex	Normal	0.340
	10 mos.	Authors' ease	Normal	0.293
	2 yrs.	Authors' ease	Secondary anemia	4.02	1.14	0.362	3.2:1
			Schüller-Christian's disease	2.40	1.33	0.250	5.3:1

[illegible]

	From du	From du	From du	Of bone
Authors' case
Calculated from analysis of dry tissue and recorded percentage of loss of water.

normal. This is probably due to a greater lipid involvement of these organs in his case (Jghanti⁶). Tissue similar to that found in the xanthoma of the skull was found in the liver and spleen. There were only a few areas of normal spleen left, while in our case the splenic involvement consisted of only a few localized areas of fibrous tissue containing foam cells. There was no lipoidosis in the liver and spleen in our case.

In Kleinman's case the phospholipoid content of the liver and spleen was much lower than that found in our case.

Kleinman spoke of a reversal of the phospholipoid-cholesterol ratio in Schüller-Christian's disease. We have been unable to determine the normal ratio of these substances in the tissues, and there are not sufficient data in the literature to establish it. The ratios that we obtained in our case of Schüller-Christian's disease and in our case of anemia were from 3.2:1 to 6.4:1, except for the heart, which showed a higher ratio (10.5:1 and 12:1).

When we compare the lipid content of the various tissues in Schüller-Christian's disease with the values for normal tissue that we have found in the literature, we are impressed with the similarity in the kidneys, liver, spleen and heart muscle. On the other hand, in the lungs the cholesterol was higher; in the skeletal muscle the total lipid and cholesterol were very low, and in the suprarenals the total lipid and cholesterol were higher. It should be remembered that the normal tissue used for comparison of values in the heart muscle, suprarenals and lungs came from the fetus, and accordingly satisfactory comparisons cannot be made. We do not know the effect of the aging process on the lipid content of the various tissues. We observe that in one case, recorded by Beumer⁷ (table 5), the total lipid content of the suprarenals of a 6 year old child was 14.6 Gm. per hundred grams of tissue, while that recorded by the same author for an 8 month fetus was only 2.9 Gm. The same wide variation is noted in the cholesterol content (1.099 Gm. as compared with 0.358 Gm. in the 8 month fetus).

Because of the severe anemia in our case of Schüller-Christian's disease we were interested to see what the comparative lipid contents of the tissues in a case of equally severe anemia not associated with xanthomatous involvement might be. These comparisons will be better seen by reference to table 5, in which we have arranged the cases together under each caption. There is a similarity in the liver, spleen, kidneys and heart muscle. In the lungs of the patients with Schüller-Christian's disease the cholesterol was higher; in the striated muscle the

6. Jghanti, W. K.: *Virchows Arch. f. path. Anat.* **282**:585, 1931.

7. Beumer, H.: *Monatschr. f. Kinderh.* **19**:409, 1921.

total lipid was lower.⁸ In these comparisons the factor of age does not enter. The comparison of the anemias may be seen in table 2; at the time of death in each case the color index was above 1 and the differential counts were similar in many ways. The blood chemistry also showed many points of similarity (table 3).

CONCLUSIONS

1. The analysis of the total lipid, cholesterol and phospholipoid content of the various tissues in a case of Schüller-Christian's disease and in one of severe anemia, for comparison, are recorded. We have also given a review of the literature on the lipid content of human tissue that could be brought into close comparison with the methods that we employed.

2. No significant changes were found in the lipid content of the tissues in the case of Schüller-Christian's disease except where the xanthomatous masses were located.

3. The xanthomatous masses had a high content of total lipid, 50 per cent of which was cholesterol. The xanthomata of the bone marrow contained an amount of total lipid and cholesterol similar to that found in the xanthomatous processes in other locations. The widespread lesions were in the bone marrow. Our observations confirm those of Epstein and Lorenz and Kleinman on xanthomata of the dura.

4. These observations record the condition of the tissues at the end of a prolonged clinical process. We know of no observations on the lipid content of the tissues in the earlier stages of the disease.

8. There was considerable edema in this tissue. The anemia in this case was of much longer duration.

ARTERITIS OF THE TEMPORAL VESSELS

A PREVIOUSLY UNDESCRIBED FORM

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Arteritis of the temporal vessels is unusual, and a new clinical syndrome, the etiology of which is still obscure, is probably represented in the two cases which form the basis of this report. These are the only cases which have been observed at the Mayo Clinic, and we have not noted reports of similar cases in the literature. A name cannot be given to this condition until more cases have been observed and the condition is dignified by nomenclature.

REPORT OF CASES

CASE 1.—An unmarried woman, aged 50, was first admitted to the clinic in May, 1917. General examination at that time gave negative results. The blood pressure in millimeters of mercury was 129 systolic and 78 diastolic. At the second admission, in September, 1927, the physical examination and laboratory tests disclosed an enlarged uterus, sclerosis, graded 1, of the retinal arteries and a blood pressure of 216 systolic and 126 diastolic. At the third admission, in December, 1927, the blood pressure was 200 systolic and 125 diastolic. The patient came the fourth time, on March 1, 1928, because she had colic of the left kidney. Cystoscopic examination revealed a stone in the left ureter, which was removed by manipulation. The blood pressure was 170 systolic and 98 diastolic. A diagnosis of fibroid uterus had been made previously, and because of excessive and irregular menses, total abdominal hysterectomy, bilateral salpingectomy, bilateral ovariectomy and appendectomy were performed. Recovery was uneventful. At the fifth admission, on June 14, 1928, the blood pressure was 230 systolic and 120 diastolic. Sclerosis, graded 1, of the retinal arteries was present. The results of laboratory tests made as a routine were negative. The patient's chief complaint at her sixth admission, on Nov. 20, 1928, was of headaches in the morning for two and a half months. Hourly observations of the blood pressure revealed a range of from 195 to 250 systolic and of from 100 to 130 diastolic. The concentration of hemoglobin was 72 per cent (Dare); erythrocytes numbered 4,890,000 and leukocytes, 5,900 in each cubic millimeter of blood. The value for urea was 25 mg. and for creatinine, 1.7 mg. in each hundred cubic centimeters of whole blood (method of Folin). The return of phenolsulphonphthalein in the urine was 50 per cent in two hours; albumin, graded 2, was present. Electrocardiograms gave evidence of left ven-

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tricular preponderance, a diphasic T-wave in derivation I and an inverted T-wave in derivations I, II and III.

Observations at the patient's seventh admission, on March 16, 1931, were of particular interest. She complained of soreness of the scalp, painful nodules along the temporal arteries, anorexia, loss of weight and headaches of six weeks' duration. She remained under observation for forty-two days. A few small, painful nodules were still present in the left temporal region, along the superficial temporal artery. They recurred from time to time during her stay in the hospital. The temperature by mouth ranged from 98 to 103 F.; the pulse rate was from 80 to 120 beats a minute. Leukocytes varied from 7,500 to 13,700, the concentration of hemoglobin was 40 per cent (Dare), and erythrocytes numbered 3,620,000. The differential leukocyte count was normal, and repeated examinations of the blood gave no additional significant findings. The general physical examination gave essentially negative results except for compensatory cardiac hypertrophy, graded 1, and retinal and peripheral sclerosis, graded 2. The patient was mentally alert, but during this period she had frequent severe headaches which differed from the morning headaches previously referred to. Otherwise she had no definite aches or pains. Hourly records of blood pressure, with the patient at rest, showed a range of from 140 to 190 systolic and of 65 to 100 diastolic. A roentgenogram of the head revealed that the sella turcica was enlarged, graded 3, and that the floor and posterior clinoid processes were eroded. Neurologic examination gave objectively negative results, as did that of the cerebrospinal fluid. The visual fields were normal. Urinalysis, made repeatedly, gave negative results except that it disclosed traces of albumin. The result of the serologic test for syphilis was negative. Cultures of the blood, made on March 27, April 9 and April 27, and cultures of the urine gave negative results. The results of inoculation of guinea-pigs with urine catheterized from the bladder were negative. In the stained sediment of the urine, bacilli of tuberculosis were not found. Agglutination for undulant fever, typhoid fever and paratyphoid fever A and B was negative. Examination of the sputum disclosed nothing abnormal. The basal metabolic rates were —15 and —12. A proctoscopic examination gave negative results. An electrocardiogram disclosed that the cardiac rate was 95 beats each minute, sinus tachycardia was present, and there were left ventricular preponderance, a notched P wave in derivation III and a slurred QRS complex in derivations I and III. Analysis of the gastric content in terms of cubic centimeters of tenth normal sodium hydroxide revealed a total acidity of 54 and free hydrochloric acid of 34. The return of phenolsulphonthalein in the urine was 70 per cent in two hours. The value for urea was 28 mg. in each hundred cubic centimeters of blood. Roentgenograms of the kidneys, ureters and bladder, right hip, thorax, stomach, small intestine and colon were negative. A segment from one of the thrombosed left temporal arteries was removed for biopsy, for cultures, and for special study, results of which will be reported later in this paper. The treatment instituted will also be discussed later.

The patient was under observation again in June, July and August, 1931. The temperature by mouth was from 99.5 to 100 F. in the afternoon, and the pulse rate was from 90 to 100 beats each minute. During this period painful nodules recurred along the temporal vessels with the usual systemic effects. The patient was hospitalized on September 23 and remained in the hospital for two days. The tenderness of the scalp and temporal regions entirely disappeared. The temperature became normal, and the blood picture improved; the concentration of hemoglobin was 11.1 Gm. in each hundred cubic centimeters of blood. Erythrocytes numbered 4,340,000 and leukocytes 6,000 in each cubic millimeter of blood. The differential

leukocyte count was normal. The blood pressure was 230 systolic and 125 diastolic. The patient remained in good health until the spring of 1932, when cardiac and renal insufficiency developed and she was hospitalized for forty days. Following this she remained well until November, 1932, when again tender areas along the left temporal artery developed.

The patient was again observed at the clinic on Dec. 3, 1932. The left superficial temporal artery was more prominent and tortuous than the right and small segments about 1 cm. in length were tender, but still pulsated. Definite nodules were not present. The walls of the vessel in the tender regions felt thicker than



Fig. 1 (case 1).—Cross-section of an occluded vessel. Marked thickening of the intima almost to the point of occluding the vessel can be observed. A granulomatous area with almost complete destruction of the media is present (a); $\times 55$.

the adjacent proximal and distal segments. The temperature by mouth was 98.2 at 11 a. m., and the blood pressure was 200 systolic and 120 diastolic. Laboratory tests were not carried out.

The patient's final admission was on Feb. 27, 1933; she came because of congestive heart failure and marked renal insufficiency. The painful areas over the scalp and along the temporal vessels had not recurred since December, 1932. She was under observation for thirty-two days, but little clinical improvement was noted. The value for urea fell from 62 mg. on admission to 32 mg. in each hundred cubic centimeters of whole blood. Daily urinalysis revealed albumin graded from 3 to 4 and a few casts. No change was observed in the ocular fundi or sella

turcica from that which was observed on the previous examinations. The visual fields were normal. Roentgenograms of the thorax revealed that the heart was enlarged, graded 4. The electrocardiogram revealed sinus rhythm, left ventricular preponderance (marked), inverted T waves in derivation I, exaggerated P waves in derivations II and III and slurred QRS complexes in derivations I, II and III. The blood pressure ranged from 160 to 190 systolic and from 80 to 130 diastolic. The patient gradually failed after she returned to her home and died approximately a month later. Necropsy was not performed.

CASE 2.—A man, aged 68, of Irish parentage, registered at the clinic on May 25, 1931. He had always had excellent health until the onset of the illness for which he sought treatment. His chief complaints were weakness and painful and tender areas over the scalp, which had been present for four weeks. At the onset pain around the teeth and stiffness of the jaw had developed. A week later pain had developed in the forehead and frontal area, with marked tenderness and a feeling of warmth in these areas. These symptoms were present daily. He did not know if the temperature was elevated. He had lost 25 pounds (11 Kg.).

Physical examination revealed that the patient was undernourished, appeared to be anemic, and weighed 140 pounds (63 Kg.). Red, raised, tender areas were present along the superficial temporal arteries. The cervical lymph nodes were moderately enlarged. Dental examination revealed periapical infection, graded 3; nine teeth were involved and pyorrhea was marked. The blood pressure in millimeters of mercury was 165 systolic and 90 diastolic. The temperature by mouth ranged from 99.3 to 100 F. Urinalysis gave negative results. The concentration of hemoglobin was 12.1 Gm. in a hundred cubic centimeters of blood; erythrocytes numbered 3,730,000 and leukocytes 10,600 in each cubic millimeter of blood. The differential leukocyte count was normal. The serologic test for syphilis gave a negative result. Roentgenograms of the thorax revealed that the heart was enlarged, graded 1. Roentgenograms of the sinuses gave evidence of a slight thickening of the membrane of the right antrum. The electrocardiogram showed that the function was normal.

A large segment of a thrombosed artery was removed from the left temporal region for cultures and special study. The infected teeth were removed during the patient's stay in the clinic. Cultures from the apexes did not reveal growth of organisms or fungi.

A letter from the patient dated Oct. 30, 1932, stated that he had had his remaining teeth extracted shortly after he returned to his home, without any untoward effects, and that he had remained well since then. There had been no recurrence of the pain along the temporal vessels.

SPECIAL STUDIES

The bacteriologic studies of the resected temporal arteries were of particular interest, and presented some significant findings.

The specimen from case 1 did not yield growth of any of the organisms which one might expect to find as contaminants, but on the third day it yielded from thirty to fifty colonies per agar unit of a rather unusual growth on the solid mediums, many different kinds of mediums having been employed. The broth cultures were sterile, again indicating lack of contamination by the ordinary bacteria. On further study it became obvious that the organism which had grown on culture

was *Actinomyces*. Sections of the artery stained with Gram stain revealed minute filamentous, gram-positive material which could easily be interpreted as being mycelia. This appearance was emphasized by the granulomatous-like lesion. At this stage in the study the second

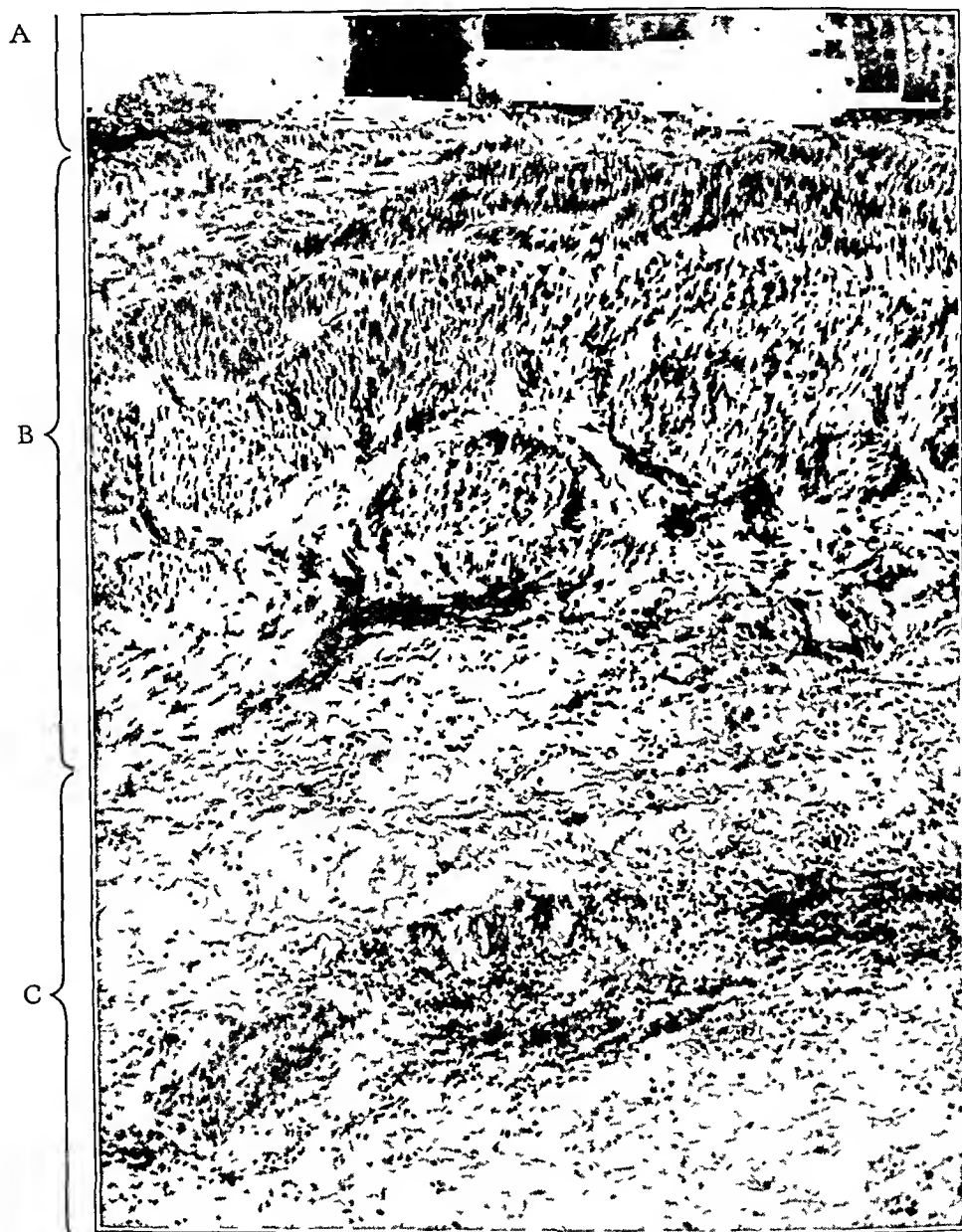


Fig. 2 (case 2).—Cross-section of occluded vessel. The lumen (*A*) is filled with an acute thrombus. Marked periarteritis with infiltration of the adventitia (*C*) with round cells is present. *B* is the media. $\times 120$.

specimen was procured and, on similar treatment, identical results were obtained. We now had two specimens from similar cases of an unusual nature yielding identical organisms of a type not usually encountered.

They differed from all other described *Actinomyces* recovered from man; in the absence of any obvious evidence of contamination, it appeared that there might be some etiologic connection between the organism found and the lesion produced. However, the *Actinomyces* found seemed to be exactly like common *Actinomyces* found in the soil and not like that found in lesions of animals. We, therefore, began a search for possible sources of contamination. Although the sand which was used to grind the organism had been sterilized at 170 C.



Fig. 3 (case 2).—Longitudinal section of a small occluded artery. The lumen (A) is filled with an acute thrombus. Marked infiltration of the adventitia (C) with round cells is present. B is the media. $\times 140$.

(338 F.) for one hour, we obtained from similar batches of sand treated in the same way and from dust in the room the same type of *Actinomyces* as we had previously found in the cultures of the two specimens. Whether the organism was introduced with the sand, whether it came from the dust of the room during the course of handling the material, or whether it was originally in the tissue, we cannot say, but the evidence is that this organism is a soil *Actinomyces*, and that it can be obtained as a contaminant under these standard conditions of procedure.

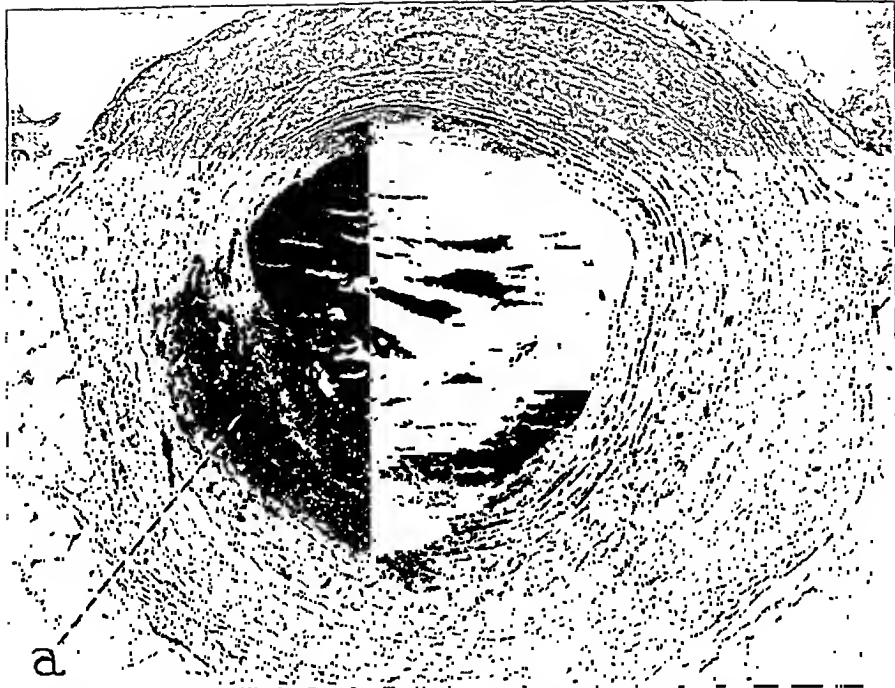


Fig. 4 (case 2).—Cross-section of an occluded vessel. The lumen is filled with an acute thrombus. Hemorrhage into the media (*a*) is seen. $\times 28$.



Fig. 5.—Higher magnification of a portion of the vessel illustrated in figure 4. Hemorrhage into the media (*a*) and a collection of lymphocytes (*b*) in the adventitia are seen.

A number of sections of blood vessels removed from patients at operation were cultured under similar technic and did not show a growth. In rabbits inoculated intravenously with the organism and in others inoculated subcutaneously along the marginal ear vessels, lesions did not develop even though some animals were observed for as long as eighteen months. These experiments cannot be considered conclusive, for it is difficult to produce actinomycosis in rabbits. This phase of the study, however, emphasizes the importance of carefully considering favorable evidence and applying fundamental principles even in the face of what appears to be positive evidence. We are unable at present to say with certainty whether this organism played an etiologic part in the disease in question.

The general impression obtained from study of the sections is that the condition is chronic periarteritis and arteritis. Peculiar, circumscribed areas of what appeared to be granulation tissue were present in the adventitia of the blood vessels and suggested granuloma; this represented the most characteristic lesion present (fig. 1). The Gram stain revealed minute, filamentous, gram-positive material in these areas which could easily be interpreted as being mycelia. In addition, infiltration of round cells was present in the adventitia around the vasa vasorum and to a slight extent in the media of the vessels (figs. 2 and 3). Hemorrhage was present in the media in some regions (figs. 4 and 5). The intima in many places was markedly thickened; the basal portion appeared acellular, and there were superimposed cellular layers, which indicated that the intimal proliferation had taken place in different stages. In other areas the thickened intima was uniformly cellular. In some sections a small lumen was still present, whereas in others the lumen had been completely occluded by either cellular or acellular thrombi.

Careful study of the affected arteries indicated that the lesion probably began as periarteritis of a small segment of the artery. When the artery was palpated at this stage, segments from 1 to 2 cm. in length were tender, but pulsations were still present. Tenderness was not present just proximal or just distal to the involved segment. What apparently happened was that the process subsided when it reached this stage, leaving the wall of the vessel thickened, but patent, or the process continued, spreading into the surrounding tissue as well as to the media and intima, with thrombosis of the involved segment. The history, clinical course, and pathologic appearance of the vessels did not suggest either periarteritis nodosa or thrombo-angiitis obliterans. We are inclined to believe that this is a newly described lesion.

COMMENT

The clinical pictures in these two cases are similar in many ways and seem to represent a definite clinical syndrome. The patients were admitted to the clinic because of similar symptoms. Microscopic study of sections of the blood vessels removed for biopsy disclosed identical lesions.

Actinomyces, species unidentified, had been found in pure culture from a small segment of the artery removed for biopsy from the first patient, approximately four weeks before the second patient had been admitted to the clinic. The similarity of the clinical features in these cases was so striking that a clinical diagnosis of actinomycosis of the temporal vessels was made in case 2. This seemed to be confirmed when *Actinomyces* was obtained in pure culture from a segment of the temporal artery. For that reason, the first patient was treated with large doses of potassium iodide for a period of four months, at which time the pain over the scalp and along the temporal vessels disappeared and did not recur for fifteen months. This patient had had no foci of infection. Marked dental sepsis, however, was present in case 2, but after all the infected teeth had been removed, the patient had remained well to the time of writing. This is of clinical interest, as *Actinomyces* often seem to gain entrance into the body by way of infected teeth. It is of interest to recall that in case 2 the first symptoms observed by the patient were pain around the teeth and stiffness of the jaw, followed a week later by pain over the forehead with the development of tender areas along the vessels of the scalp. The history suggests an infection of some type, with focal localization in the arteries of the scalp. The reasons why a diagnosis of actinomycosis cannot be said to have been confirmed have been stated.

From the clinical standpoint, too little is known of arteritis, and the pathologic criteria are not as yet well established. The types of arteritis which stand out as clinical entities are as follows: (1) thrombo-angiitis obliterans, which is the best known of these disease entities; the description of this by Buerger¹ and the confirmation of his work by many workers² have removed from the literature many diverse, heterogeneous types and have put them in one category, and (2) periarteritis nodosa,

1. Buerger, Leo: *The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor and Trophic Disorders*, Philadelphia, W. B. Saunders Company, 1924.

2. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: *Thrombo-Angiitis Obliterans: Clinical, Physiologic and Pathologic Studies*, Philadelphia, W. B. Saunders Company, 1928.

or Kussmaul's disease, which was described by Kussmaul and Maier³ in 1866, and is probably a pathologic and clinical entity. In this disease periarteritis, with acute, subacute and chronic stages, is present; in the adventitia are nodular formations composed of polymorphonuclear leukocytes and eosinophils. There is a predilection for involvement of the smaller arteries of the viscera rather than of the peripheral bed. The symptoms are largely those caused by ischemic neuritis.

Recently, Libman and Sacks⁴ described certain changes in the smaller arteries in cases of verrucous or indeterminate endocarditis. However, this arteritis may occur independently of endocardial involvement. The lesion in the capillaries and arterioles indicated active proliferation and necrosis. There was occlusion by proliferative and disintegrating cells. At times, intimal granulomas were observed. Acute arteritis has been described by von Glahn and Pappenheimer⁵ in rheumatic fever. This is probably a secondary form. Arterial changes, including various reactions of the arteries, have been described in many diseases, including typhoid fever, typhus fever, rheumatic fever, cholera, bacterial endocarditis and mycotic disease. There is also an ulcerative form observed in arteries contiguous to acute abscesses.

SUMMARY

Two patients, a woman aged 55 and a man aged 68, were observed at the Mayo Clinic in the spring of 1931, because of fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and painful, tender areas over the scalp and along the temporal vessels. The symptoms had been present from four to six weeks. Localized periarteritis and arteritis were present in each case. Relapses or complete remissions had occurred in both. Study of the microscopic sections of the blood vessels removed for biopsy disclosed identical lesions. Both patients apparently recovered completely from the local condition although one died approximately two years later from congestive heart failure and renal insufficiency. Results of bacteriologic studies are reported, but these are inconclusive. This report may represent a new clinical syndrome the etiology of which is still obscure.

3. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch. f. klin. Med.* **1**:484 (March 28) 1866.

4. Libman, Emanuel, and Sacks, Benjamin: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33**:701 (June) 1924.

5. von Glahn, W. C., and Pappenheimer, A. M.: Rheumatic Diseases of Auricle and Blood Vessels, *Tr. A. Am. Physicians* **43**:203, 1928.

GENERALIZED THROMBO-ANGIITIS OBLITERANS

REPORT OF A CASE WITH INVOLVEMENT OF RETINAL VESSELS AND SUPRARENAL INFARCTION

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There is a group of vascular diseases about which little is known, which frequently must be passed without recognition and which may often be submerged beneath and masked by other more obvious lesions. This is the class of generalized, nonspecific, chronic arteritis and phlebitis of which Buerger's disease undoubtedly is a type. Reports of thrombo-angiitis obliterans affecting vascular territories other than the extremities are accumulating. Barron and Lilienthal¹ attempted to direct attention to the more general distribution of the disease in contradistinction to what was previously believed concerning it—that it was a disease involving the blood vessels of the extremities exclusively. In substantiation of this hypothesis, they reported cases of their own and those from the literature. Taube² recently reported two cases of mesenteric involvement and collected the reports of twenty-six others which appeared in the literature and which deal with the process as it occurs in the spermatic, cerebral, carotid, aortic, coronary, mesenteric, celiac and other vessels. Barker³ reported a case in which diffuse, non-specific arteritis of the smaller arteries was found. There were recent thrombosis of the internal iliac veins, infarctions of the lungs and similar conditions. The essential lesions were scattered about in various organs. In the smaller arteries there was a peculiar obliterating type of endothelial proliferation of a rather striking degree without involvement of the media. No cause could be found. In all of the cases the lesions were marked and advanced. Furthermore, in all but the last they

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1. Barron, M. E., and Lilienthal, H.: Thrombo-Angiitis Obliterans: General Distribution of the Disease, *Arch. Surg.* **19**:735 (Oct.) 1929.

2. Taube, N.: Mesenteric Involvement in Buerger's Disease, *J. A. M. A.* **96**:1469 (May 2) 1931.

3. Barker, N. W.: Diffuse Arteritis of Unknown Etiology, *Proc. Staff Meet., Mayo Clin.* **7**:173, 1932.

were apparently uneven in their distribution and appeared to have a regional dispersal.

It is reasonable to suppose that the disease is not thought of often enough as generalized, that its manifestations have been overlooked, and that it may more frequently lie at the foundation of other entities, especially as it inherently possesses potentialities of protean modes of expression.

We report a case which presents many unusual and highly interesting features. The vascular changes, the peculiar fibrosis of the lungs, the bilateral infarction of the suprarenal glands and the alterations in the retinal vessels stand out as the most important findings. Were it not for the suprarenal insufficiency, which may be regarded as incidental, the issue would probably not have been fatal so early in the course of the disease, and the pathologic study would have been deferred to a later stage.

REPORT OF CASE

History.—C. E., a single man, aged 19, when first seen complained of intermittent pain and swelling of the legs of a year's duration. A year previously, a hard, painful swelling in the region of the left calf gradually developed. It lasted for about three weeks, necessitating rest in bed, and then it gradually subsided. For the next three months the patient was ambulatory, but did not regain his sense of well-being. Then another painful swelling, on this occasion in the region of the right calf, appeared and remained for three weeks. Six weeks before entry there was a gradual involvement of the left thigh and groin. It persisted for two weeks. About four weeks before entry the patient began to have gas pains in the lower portion of the abdomen, which became very severe; they were of a cramping, colicky nature and were accompanied by nausea and vomiting. The last two continued for three days, and the pain for three weeks. During the second week it was noted that the patient had fever, and that a slight jaundice had occurred. He entered the hospital at this time, and shortly afterward a sudden, sharp pain of a pleuritic nature developed in the right anterior region of the chest. This was followed by cough and blood-streaked sputum. During a stay of ten days in the hospital, the abdominal pain was improved, the jaundice cleared, and the cough and sputum were relieved. The patient returned home. He noticed a slight difficulty in vision on occasions during this period. Two days later he began to have pain, tenderness and swelling of the right thigh and groin. All movements of the right hip were painful. The patient returned to the hospital. He believed that he had lost about 50 pounds (22.7 Kg.) during the six weeks before entry. Except for the fact that he smoked from twenty to thirty cigarets a day, the past history and family history were noncontributory. He said that he had not had a syphilitic infection.

Physical Examination.—The patient was a fairly well developed but poorly nourished man who appeared acutely ill and complained severely of pain in the right thigh. The skin was hot, dry and flushed. Several small, discrete lymph nodes were palpated in the right posterior cervical region and several soft nodes, about 1 cm. in size, in the left groin. The conjunctivae showed a subicteric tint. The pupils were small, equal and active. The fundi showed that the arteries were very tortuous, with dilatation and streaking near the disks. The veins were

tortuous and dilated, and depressed by the crossing arteries. The cilio-retinal vessels were enlarged. The lips were dry and cracked. The tongue was coated. The lungs disclosed diminished expansion at the right base, increased vocal fremitus, harsh breath sounds and no râles. The heart was not enlarged. The sounds were of poor quality. The rate was 120, and the rhythm regular. There were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The abdomen was full and symmetrical. Much gas and borborygmi were evident. There was slight voluntary guarding over the entire abdomen. There was definite tenderness just above the right inguinal ligament. The spleen, liver and kidneys were not felt. The external genitalia were normal. Rectal examination showed nothing of importance. The right leg was held in abduction, external rotation and flexion. Passive movement caused severe pain, which was maximum over the inner aspect of the thigh along the course of the saphenous vein. Palpation of this area caused pain. There was no increased redness or heat. The right leg and thigh were one-third larger than the left. The swelling was slightly pitting. The left leg appeared to be normal. Peripheral pulsations were equal and normal in all respects. The reflexes of the triceps and biceps and the radial reflexes were equal and active. The patellar reflex was absent on the left side; it was not tried on the right. The Achilles reflex was absent bilaterally.

Laboratory Examination.—Hemoglobin was 7.5 Gm. per hundred cubic centimeters of blood (54 per cent, Sahli). The red blood cells were 2,690,000; the white cells varied from 8,000 to 18,000 with from 80 to 89 per cent polymorphonuclears. The specific gravity of the urine was 1.020 on entrance. The albumin and sugar were normal. There were 1 or 2 epithelial cells and in each high power field, 2 or 3 pus cells in the sediment and from 1 to 3 hyaline casts. Many of the hyaline casts contained as many as 12 epithelial and pus cells. A few were finely granular; rarely was a coarsely granular cast found. The bile was normal. Urobilinogen was present. According to the Volhard tests, the specific gravity varied from 1.009 to 1.011. The Addis concentration test showed a cast count of 13,000 for the total volume. The red blood count was 26,000 for the total volume. The white blood cells and epithelial cells numbered 222,000 for the total volume. The clearance test for urea and the phenolsulphonphthalein test showed nothing abnormal. The sedimentation time was seventeen minutes. Retractility of the clot was normal. All other tests, including the Wassermann test, were negative, and blood cultures showed nothing abnormal.

Roentgen studies revealed increased density in the outer lower part of the right upper lobe. A roentgenogram of the chest taken eighteen days later revealed an additional change in the form of a spherical shadow which was interpreted as a small cavity.

The diagnosis most often suggested was multiple thrombophlebitis on an infectious basis. An unusual form of thrombo-angiitis obliterans was mentioned on the first day of hospitalization.

Course.—The temperature on entry was 39.2 C. (102.5 F.), but on the next day it dropped to 37.8 C. (100 F.) and the patient felt much better. For the first eight days the patient seemed to improve, the temperature remaining below 37.5 C. (99.5 F.) and the abdominal complaints being relieved. The pain and the swelling of the right thigh gradually improved, and the patient was able to move the leg freely without feeling discomfort. On the eighth day he complained of a dull, aching pain at the margin of the left rib in the midaxillary line. There was no guarding of the left upper quadrant, but on deep palpation the patient complained of tenderness. The spleen was not felt. On the tenth day the fever

began to rise and gradually reached a level of around 39 C. (102.2 F.), where it remained until death. The patient became irritable and complained a great deal. On the fourteenth day spontaneous thrombosis of the right antecubital vein occurred. On the fifteenth day in the hospital, signs of meningeal irritation developed. A lumbar puncture was performed, and the findings were negative. This suggested meningismus. The patient continued to lose ground. On the nineteenth day the blood pressure was 100 systolic and 60 diastolic. On the twentieth day the patient became comatose. A transfusion of 300 cc. of whole blood was given without benefit. On the twenty-first day the coma became deeper, and the patient died of heart failure.

Postmortem Examination.—Postmortem examination was performed one hour after death. The lungs lay in the normal positions. The right pleural cavity was obliterated posteriorly over the lower lobe and inferiorly by adhesions between

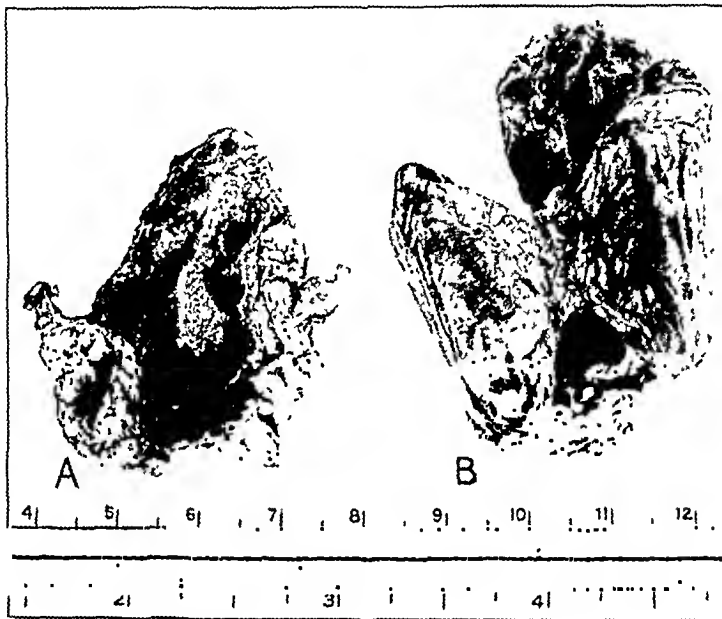


Fig. 1.—The suprarenal glands. *A* represents the right gland; *B*, the left.

the parietal, visceral and diaphragmatic layers. The posterior adhesions were rather recent and could be easily broken by the examining finger. The adhesions on the lower portion of the lobe were much more firm and dense. On the surface of the upper part of the right lower lobe was a rectangular area which measured about 4 by 4 cm., over which the pleura was roughened and covered with fine adhesions. Deep in this area there appeared an infarcted block of pulmonary tissue in which there was a rounded, brownish, necrotic plug. Above this there was a small, empty cavity which measured about 1 cm. in diameter. The lungs felt rather firm and did not seem so crepitant or so elastic as normally. Examination of the heart revealed nothing unusual. The left suprarenal gland was perhaps three or four times as large as normal. It weighed 29 Gm. Its cortex was thinned to the extent of remaining as only a shell. Its medulla was destroyed and replaced by firm, reddish-brown, hemorrhagic material. The right suprarenal gland was smaller than the left, and weighed 17 Gm. It presented a picture not unlike that of the left side except that here the infarction was recent, and the medullary portion was filled with a red, friable hemorrhagic coagulum and was partly cavitated (fig. 1). The aorta was smooth and elastic. It con-

tained rare, early atheromatous plaques. The saphenous vein in the right leg was found to have thickened walls and to contain an antemortem organizing thrombus. It was readily pulled from its sheath. The smaller arteries throughout the body appeared grossly to have thickened walls, and close examination revealed that minute thrombi filled the lumens of a few. This held true for most of the vessels examined, including those at the hilus of the liver, the kidney, the spleen, the branches of the gastric and pancreatic arteries, the prostatic vessels and the basilar cerebral vessels. Sections were taken from all of the vessels for microscopic examination.

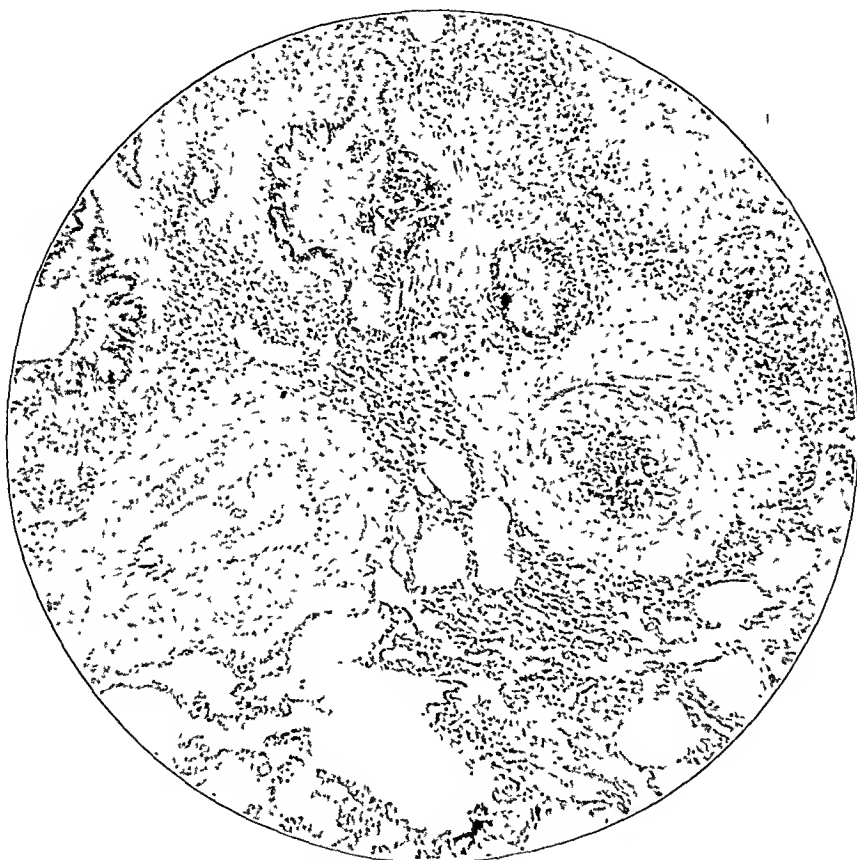


Fig. 2.—Microscopic section of the lung. Note the peribronchial and perivascular fibrosis. The vascular changes found elsewhere are seen here, with thrombosis. The increase in the connective tissue in the alveolar septa is seen.

Microscopic Examination.—Sections were studied from nine blocks of tissue removed from various parts of the lungs. The alveolar walls were found to contain an increased amount of connective tissue. They were thickened and stiffened because of the fibrosis. About most of the bronchi and blood vessels were collars of fibrous tissue through which broad, cicatricial bands were occasionally observed to course. The blood vessels displayed striking alterations, to be described (fig. 2). The infarcted areas contained degenerating or necrotic centers in which the faint shadows of the original pulmonary architecture could still be perceived. Surrounding the regions was a dense, fibroblastic border. Hemorrhage was frequently seen and in places was undergoing organization. The

alveoli throughout the lungs held numerous large endothelial cells which contained granules of brown pigment. There was no evidence of either a pneumonic or a tuberculous process. The myocardium showed early degenerative changes marked by fatty infiltration, fraying of the fibers and loss of transverse striation. No Aschoff bodies were found. Sections of the liver were punctuated throughout with small areas of focal necrosis. They showed moderate passive congestion. The mesenteric lymph nodes displayed a rather marked degree of follicular hyper-

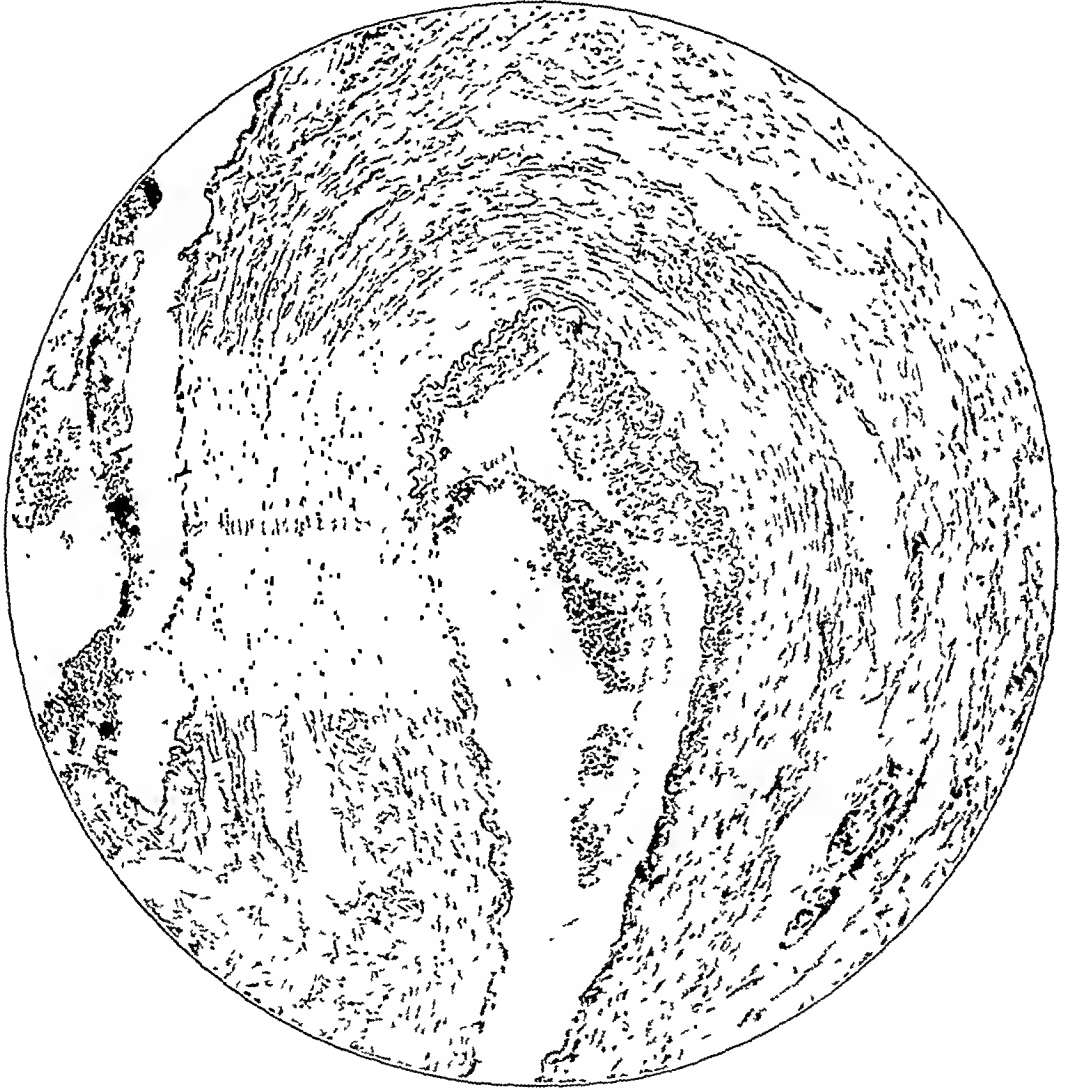


Fig. 3.—A branch of the coronary artery, showing especially the intimal thickening.

plasia. The suprarenal glands presented striking changes. Their capsules were increased in thickness in an irregular manner with an increase in connective tissue and considerable fatty infiltration. Occasional foreign body giant cells were seen in clusters external to the parenchyma. There was some lymphocytic infiltration. The right suprarenal gland was filled with recent hemorrhage. The medulla was entirely destroyed, and only occasional patches of the glomerular stratum or the uppermost cells of the vesicular portion were seen. The process on the left seemed to be older and was in the nature of an anemic infarct with

the suprarenal substance represented by the shadows of the original architecture. In the pituitary gland there was apparently an increase in the number of basophilic cells throughout. In the central portion of the pars distalis was a circumscribed area occupying about three fourths of a low power field which was composed entirely of groups of cells of the basophilic type. It was not encapsulated and may have been a miliary area of hyperplasia rather than a true adenoma. In all of the smaller arteries as well as in some of the veins there were pathologic

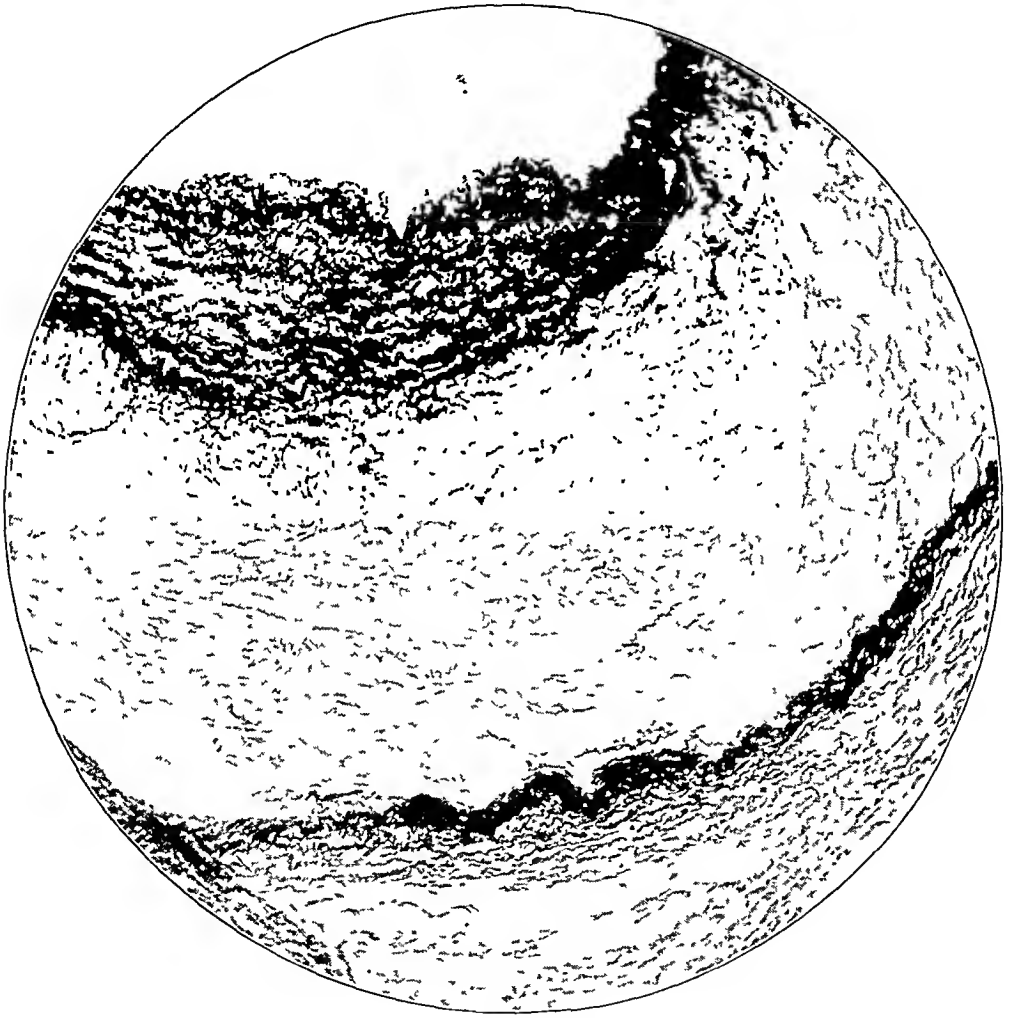


Fig 4—A branch of the pancreaticoduodenal artery. Note the marked reduplication of the internal elastic lamina. Weigert's elastic tissue stain; $\times 450$.

changes (figs. 2, 3, 4 and 5) The small arteries were particularly affected. The very smallest vessels, except those distal to an actual thrombus, did not appear to be involved, nor was the aorta or most of its major branches. The adventitia showed an increased amount of connective tissue which extended in many places into the surrounding tissue. Occasionally small groups of lymphocytes or plasma cells were caught in it, suggesting a more active process at an earlier time. The fibrosis at times reached adjacent epineuria and included the neighboring veins. For the most part, however, it was confined to merely an adventitial thickening. The media contained rare plasma cells. The muscle was well preserved, although

it was somewhat hyperplastic. There was no increase in the connective tissue or fibrous replacement of the muscularis. The intima was the site of a proliferative process, and had undergone hyperplasia in an irregular manner so that it encroached on the lumen and narrowed it considerably. The proliferation did not progress to the point of actual obliteration but seemed to pave the way for the formation of a thrombus which was found in many places. The cells of the intima had a circumferential distribution. There was occasional vacuolation or a foamy appearance. The internal lamina (fig. 4) was moderately increased.

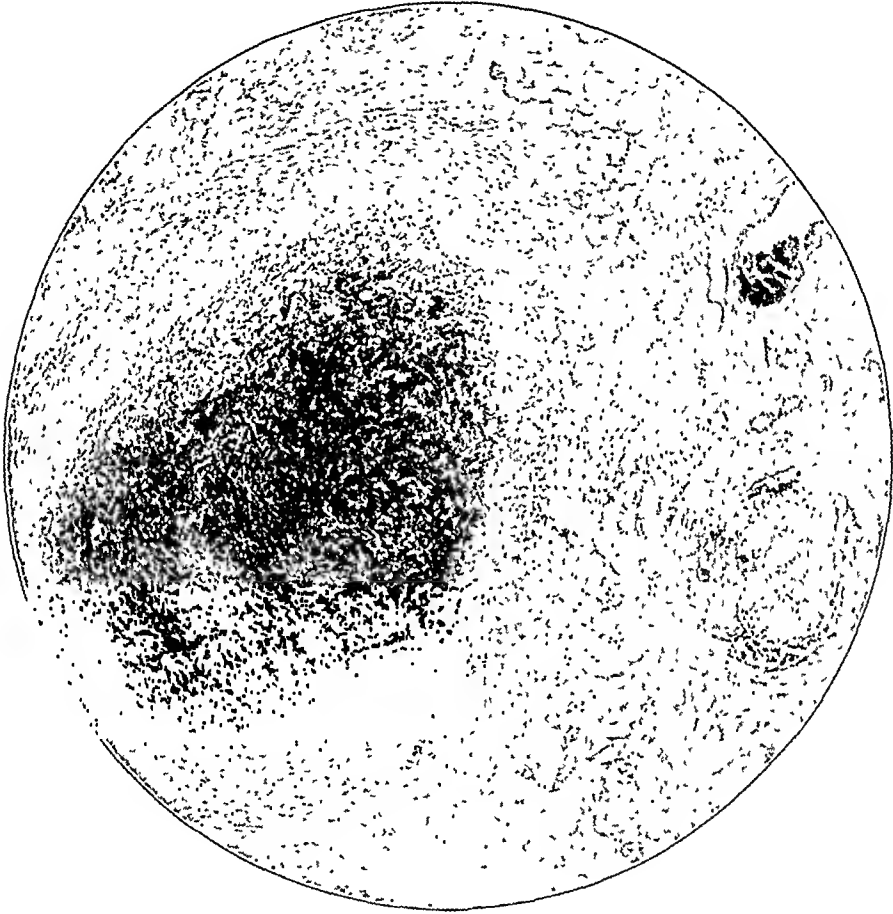


Fig. 5.—Vessels in the region of the urinary vesicle, neck and prostate. Obliterating thrombosis is present in both vascular channels. Hematoxylin and eosin stain; $\times 100$.

The elastic fibers were reduplicated and concentric. Most of the thrombi had advanced to a stage of organization and canalization. Sections of the saphenous vein showed panphlebitis with organizing thrombosis.

COMMENT

The pathologic process in the vessels is perhaps the basic finding. For the time, the condition must be regarded as of obscure etiology. In reviewing the pathologic histology of the vessels, one must consider the various lesions affecting the circulatory system in a like manner. Among these may be mentioned the endarteritis obliterans of Virchow,

thrombophlebitis migrans, syphilitic arteritis (including Heubner's endarteritis), thrombo-angiitis obliterans, rheumatic angiitis and periarteritis nodosa. Just as most of the conditions have many points in common, so does the process under consideration resemble and differ from each of these conditions in one or more respects. As may be seen from the microscopic description, if one is to employ a descriptive diagnosis, one is forced to choose thrombo-angiitis obliterans, as only this term adequately covers the principal elements of the vascular lesions.

The periarterial, early lymphatic infiltration and the later thickening and fibrosis of the adventitia which tend to mat the neighboring nerve and vein to the artery are as a rule marked in thrombo-angiitis obliterans.⁴ In this case, however, although the fibrosis was universal and occasionally included groups of lymphocytes and plasma cells, it was only of moderate degree. The venous sheaths and perineuria were only rarely reached, and then not to an extent which could have been noted grossly. The media of the vessels in this case showed the least changes. Aside from the fact that it was thickened, it was not remarkable, nor was the increase in thickness accomplished by fibroblastic proliferation but rather by an apparent muscular hypertrophy. In thrombo-angiitis obliterans there is usually an increase in the connective tissue of the media; in periarteritis nodosa, necrosis, fibrosis and hyalinization; in rheumatic arteritis, vacuolation and death of the muscle, and so on. No attempt at formation of a collateral circulation through the vasa vasorum in the media such as is discovered in some of these conditions was noted here. Except for the marked thrombus formation found in this case before the lumen had been narrowed to any considerable degree, the intimal changes are strongly reminiscent of endarteritis obliterans.

Warthin^{4b} described changes in the smaller arteries in a case of syphilis in which there was thickening of the intima with hyaline changes but without infiltration and in which no spirochetes were found. He observed that the vessels became concentrically thickened through proliferation, and that the lumen was obliterated by fibroblastic tissues. This was especially well noted in the vasa vasorum of the aorta. Heubner described these alterations, especially in the central nervous system. In our case there is no evidence of a syphilitic process, and it is particularly to be observed that the large vessels are spared. It is the smaller arteries and not the very small nor the major channels which are involved.

4. (a) Brown, G. E., and Allen, E. V.: *Thrombo-Angiitis Obliterans*, Clinical, Physiologic and Pathologic Studies, Collaborating in Pathology with H. R. Mahorner, Philadelphia, W. B. Saunders Company, 1926. (b) Warthin, A. S.: *Syphilis of Medium and Smaller Arteries*, New York M. J. **115**:69, 1922.

The condition known as thrombo-phlebitis migrans has found its way into recent literature, especially on the continent and in England.⁵ Little pathologic study has been accorded it. It usually appears in small lengths of the superficial peripheral veins and frequently in the lungs and the abdomen. The heart and the brain are more rarely affected. The disease is characterized by a long course with frequent febrile exacerbations. Since the prognosis is favorable and not more than a score of cases are reported, the opportunity for study at autopsy is infrequent. The cases reported by Moorehead, Abrahamson, Eyle, Ellison and others were, as the name suggests, principally evidenced in the veins and did not clinically point to the arterial tree, as in our case.

The lesion in the lung is of itself unusual. It is, no doubt, to be explained on a circulatory basis dependent on a pulmonary oligemia and on actual infarction due to thrombosis of the arteries. In 1929, Frothingham⁶ reported a case similar in many respects, so far as the lungs are concerned, to our case. Extensive fibrosis of the alveolar septums, many of which were almost avascular, a peculiar peribronchial and perivascular increase in connective tissue, thrombosis of the smaller arteries and infarctions of the lungs were found. Many other cases of nonspecific pulmonary fibrosis have been reported, such as the eighteen cases reported by Posselt⁷ and those of Schütte⁷ and of Eppinger and Wagner.⁷ For the most part, the larger arteries showed involvement, too, as in Ayerza's disease, but some of the lesions were confined to the smaller vessels in the lungs, except in Frothingham's case, in which thromboses were present in the uterine and vaginal vessels. No mention was made of the presence or absence of vascular changes elsewhere in the body in vessels of the same size.

Because the clinical manifestations in this case were so widespread, it would be well to try to correlate them with the pathologic findings. The painful swellings in the calves of which the patient first complained were undoubtedly due to thrombophlebitis of the veins of the lower extremity. The severe attack of cramplike abdominal pain, nausea and vomiting was probably a result of the involvement of mesenteric vessels with the resulting ischemia of the bowel. The icterus was no doubt on a basis of hepatic focal necrosis which may have been a result of the involvement of the hepatic vessels. The pleuritic pain followed by cough and hemoptysis is related to the pulmonary thrombosis. Barker⁸

5. Barber, H.: Thrombo-Phlebitis Migrans, *Brit. M. J.* **1**:281 (Feb. 13) 1932. Moorehead, T. G., and Abrahamson, L.: Thrombo-Phlebitis Migrans, *Brit. M. J.* **1**:586 (April 7) 1928.

6. Frothingham, C.: A Case of Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Arteries, *Am. J. Path.* **5**:11, 1929.

7. Quoted by Frothingham.⁶

8. Barker, N. W.: Thrombo-Angiitis Obliterans with Occlusion of Both Femoral Veins and Both Popliteal Arteries, *M. Clin. North America* **15**:233, 1931.

described a case with pulmonary embolism in a patient with thrombo-angiitis obliterans. The difficulty of vision in our case was probably due to the involvement of the retinal vessels. The fever and the evidence of peritoneal irritation followed by the prostration which the patient suffered during the last few days of life were undoubtedly due to suprarenal infarction.⁹ Fever has been found to be an almost constant feature of suprarenal apoplexy. The clinical features of epigastric pain and tenderness followed by prostration and feebleness of the pulse terminating in death fit in well with Lavenson's¹⁰ peritoneal type of suprarenal hemorrhage. He and others found that this was the most common type of reaction found in this rare condition.

The urinary findings and the results of the tests of renal function are of interest. On entry the specific gravity of the urine was 1.020. Later there was inability to concentrate above 1.011. The urea clearance and phenolsulphonphthalein tests were within normal limits. However, there was a definite increase in casts as determined by the Addis concentration test. Many of these casts were remarkably cellular, and as many as 12 cells were found in some of them. These changes are probably due to the involvement of the smaller arteries of the kidney. It is interesting to speculate on the future progress of these changes in the kidneys had the patient not died. Because of the wide extent of the renal arteriolar involvement, further degrees of renal insufficiency would most probably have occurred. The marked meningismus and terminal external strabismus must have been due to the involvement of the cerebral vessels. Nervous symptoms such as convulsions, coma and typhoid states, following suprarenal apoplexy have been described by Lavenson, but meningismus has not been mentioned as a manifestation of suprarenal apoplexy. The prolonged clotting time is of interest, since Steel¹¹ believed that the coagulation time was shortened in this condition. Secondary anemia has been found by Brown^{4a} to occur in the more fulminant types of thrombo-angiitis obliterans. Leukocytosis is an unusual finding without secondary infection. The rapid sedimentation time may indicate that an infectious process of some type is the cause.

The hemorrhagic infarction of the suprarenal glands may no doubt be explained on a thrombotic basis. Just why the suprarenal glands (or the lungs, for that matter) should have been chosen, it is difficult to say. However, it is to be noted that there was an uneven degree of

9. Seligman, B.: Suprarenal Hemorrhage in the Adult, *M. J. & Rec.* **135**: 209 (March 2) 1932.

10. Lavenson, R. S.: Acute Insufficiency of the Adrenals, *Arch. Int. Med.* **2**:62 (Aug.) 1908.

11. Steel, W. A.: Intravenous Citrate of Soda Treatment of Thrombo-Angiitis Obliterans, *M. Rec.* **99**:370, 1921.

involvement throughout the vascular tree. According to Goldzieher,¹² if the larger medullary vein or central veins of the suprarenal glands are thrombosed, hemorrhagic infarction is inevitable. This has been studied experimentally by Martinotti and Torrini,¹³ who ligated the central vein. In less than twenty-four hours they found marked alteration in the cortical cells, the changes in those of the medulla being less striking. It is interesting to note in this connection that Torrini found that unilateral ligation of the central vein which is followed by stasis, thrombosis and hemorrhagic infarction on the side on which the ligature has been applied frequently gives rise to a similar process on the opposite side, which has not been touched. The mechanism of this sympathetic infarction may be explained on a similar basis. The difference in age in the suprarenal changes found in our case are compatible with such an explanation. Of course hemorrhage and infarction of the suprarenal glands may occur in a score of conditions, such as trauma, severe venous congestion and generalized infection or intoxication, but it is not necessary to postulate such a basis in this case. We have been unable to find another case of suprarenal apoplexy resulting from thrombo-angiitis of the suprarenal vessels.

Brasser,¹⁴ however, described a case of suprarenal apoplexy in which there was an old thrombosis of the saphenous vein, and he thought that a constitutional defect in the blood vessels might have predisposed to the thrombosis in his case. Brasser, Bittorf,¹⁵ Simmonds¹⁶ and Pearl and Brunn¹⁷ also described cases in which there was evidence of thrombosis elsewhere in the body. In none of these cases, however, was there evidence of thrombo-angiitis obliterans.

The changes in the retinal vessels are of particular importance from a clinical standpoint, as they are the only ones that can be seen and therefore offer an important clue to the diagnosis. Our patient complained of slight difficulty in vision, which probably resulted from these changes. Grasser¹⁸ described involvement of the retinal vessels in a typical case of Buerger's disease in which there was complete loss of

12. Goldzieher, N. A.: *The Adrenals: Their Physiology, Pathology and Diseases*, New York, The Macmillan Company, 1929.

13. Martinotti and Torrini, quoted by Goldzieher.¹²

14. Brasser, A.: *Beitrag zur Kenntnis der Nebennierenerkrankungen*, Klin. Wchnschr. **3**:738, 1924.

15. Bittorf, A.: *Zur Kenntnis der Nebennierenerkrankungen*, München. med. Wchnschr. **73**:1928, 1926.

16. Simmonds, M.: *Ueber Nebennierenblutungen*, Virchows Arch. f. path. Anat. **170**:242, 1902.

17. Pearl, F., and Brunn, H.: *Suprarenal Apoplexy, Bilateral*, Surg., Gynec. & Obst. **47**:393, 1928.

18. Grasser, E. B.: *Partial Occlusion of the Retinal Vessels in Thrombo-Angiitis Obliterans*, Am. J. Ophth. **15**:235, 1932.

vision. The ophthalmologic examination revealed conditions similar to those found in this case. Changes in the retinal vessels have been found in other generalized vascular diseases, such as periarteritis nodosa, Raynaud's disease and arteriosclerosis. The alterations in the latter conditions are known and can be easily differentiated from those described in this case. In periarteritis nodosa, aneurysmal dilatations of the retinal arteries have been described. In Raynaud's disease spasm of the retinal arteries has occasionally been noted. In arteriosclerosis, the retina is often involved, the changes in the veins are not so marked, and there is not so much dilatation of the vessels as there was in this case.

SUMMARY

1. An unusual case of generalized vascular disease, probably early thrombo-angiitis obliterans, in which autopsy was possible early in the course because of the involvement of vital structures (the suprarenal glands) is reported.

2. Involvement of the cerebral, retinal, pulmonary, coronary, mesenteric, suprarenal, pancreatic, duodenal, hepatic, renal and prostatic vessels and of the vessels of the extremities was found. The clinical manifestations of the changes and of the suprarenal apoplexy in this case are discussed.

3. The possibility that thrombo-angiitis obliterans is more frequently a generalized disease is pointed out.

RELATION OF THE PLASMA CHOLESTEROL TO OBESITY AND TO SOME OF THE COM- PLICATING DEGENERATIVE DISEASES

(DIABETES MELLITUS, ESSENTIAL HYPERTENSION, OSTEO-ARTHRITIS
AND ARTERIOSCLEROSIS)

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Studies of the cholesterol content of the plasma in the obese and the influence that several associated clinical conditions have on it are reported in this paper. It is important to know whether the excessive indulgence in food by human beings over a long period is associated with a rise in the cholesterol content of the blood. The relation between obesity and essential hypertension, diabetes mellitus and arteriosclerosis has been stressed for many years; the increased blood cholesterol in the latter three diseases has been frequently observed by many workers. Because of these facts, a critical investigation of the relationship between the blood cholesterol and the body weight and the degenerative diseases supposedly resulting from obesity suggested itself. Oddly enough, we were unable to find a single study in the literature in which these aspects of the subject were investigated; the published records given herewith were usually part of a related problem.

LITERATURE

Denis¹ stated that the plasma cholesterol is elevated in cases of obesity; she remarked, however, that each of the two subjects in her normal group who had the greatest weight showed a low plasma cholesterol. Epstein and Lande² believed obesity to be one of the condi-

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1. Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, *J. Biol. Chem.* **29**:93, 1917.

2. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: I. The Relation of Cholesterol and Protein Deficiency to the Basal Metabolism, *Arch. Int. Med.* **30**:563 (Nov.) 1922.

tions associated with a high blood cholesterol. Labbé and Heitz³ reported six cases of obesity with an associated hypercholesteremia. Weil, Guillaumin and Abricosoff⁴ studied twenty-four obese subjects; sixteen showed a high blood cholesterol, and eight, normal values. Koning⁵ reported ten cases of obesity, in each of which there was a distinctly elevated blood cholesterol. It should be stated that the obese subjects studied by Weil and his co-workers and by Koning usually had an associated disease, such as hypertension, arthritis, gout and diabetes mellitus. Waldorp⁶ and Petersen and Levinson⁷ recorded cases of obesity complicated by hypertension or endocrine dysfunction in which the plasma cholesterol was moderately elevated.

White and Hunt⁸ stated that overnutrition in the diabetic child is associated with a high plasma cholesterol. Bing and Heckscher⁹ studied five cases of obesity and found that the blood fat was greatly increased (twice the upper normal limit). Likewise, Gray¹⁰ showed that diabetic patients who were overweight or near the normal weight had a tendency toward elevated blood fat.

Bonnefous and Valdiqué¹¹ and Laurentier and Valdiqué¹² found that the cholesterol content of the blood was consistently elevated in ten cases of lipomatosis. Strauss and Schubardt¹³ reported cholesterol studies in one hundred and sixty patients with various diseases; one case of lipomatosis showed an elevated blood cholesterol.

3. Labbé, M., and Heitz, J.: La cholestérinémie des diabétiques, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1546, 1924.

4. Weil, M. P.; Guillaumin, C. O., and Abricosoff, L.: Contribution à l'étude du sang des obèses, l'état de pléthore, *Ann. de méd.* **23**:328, 1928.

5. Koning, J. W.: Het cholestearine-gehalte van het bloed bij verschillende ziekten, *Nederl. tijdschr. v. geneesk.* **66**:540, 1922.

6. Waldorp, C. P.: Relaciones entre la hipertensión arterial primitiva (genuina o esencial), enfermedades de la nutrición y sistema endócrinovegetativo, *Semana méd.* **35**:609, 1928.

7. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of Normal Men and of Clinical Patients: III. Detailed Study of the "Normal" Group and of Miscellaneous Clinical Patients, *Arch. Path.* **9**:198 (Jan.) 1930.

8. White, P., and Hunt, H.: Cholesterol of the Blood of Diabetic Children, *New England J. Med.* **202**:607, 1930.

9. Bing, H. I., and Heckscher, H.: Untersuchungen über Lipämie: III. Pathologische Verschiebungen der Blutfettmenge, *Biochem. Ztschr.* **149**:90, 1924.

10. Gray, H.: Lipoids in 1,000 Diabetic Bloods with Special Regard to Prognosis, *Am. J. M. Sc.* **168**:35, 1924.

11. Bonnefous, R., and Valdiqué, A.: Hypercholestérinémie et lipomatose, *Ann. de dermat. et syph.* **5**:290, 1924.

12. Laurentier, C., and Valdiqué, A.: Lipomatose et hypercholestérinémie, *Ann. de dermat. et syph.* **8**:297, 1927.

13. Strauss, H., and Schubardt, W.: Ueber den Cholesteringehalt des Blutserums, *Zentralbl. f. inn. Med.* **43**:425, 1922.

On the other hand, several studies have been recorded in the literature in which the blood cholesterol in obese subjects was found to be normal or low. Blix¹⁴ studied five cases in which there was a normal cholesterol value; he emphasized the fact that when an elevated cholesterol is found in an obese subject, an underlying disease, such as an endocrine imbalance, may be responsible for the hypercholesteremia. Rony and Levy¹⁵ reported the results for eighteen obese and fifteen normal subjects; the blood cholesterol averaged 128 mg. per hundred cubic centimeters in the obese and 132 mg. in the normal patients. In a personal communication to Gray,¹⁶ Luden stated that one case of obesity (390 pounds [177 Kg.]) which she studied showed a blood cholesterol of 130 mg.

MATERIAL AND METHODS

The material for this study was obtained from the clinic for obesity of the outpatient department of the New York Post-Graduate Hospital. Single studies of the blood were made on the day the patients were admitted to the clinic. In every case the blood was taken in the morning; in most instances the patients had previously eaten their customary breakfasts.

The experimental and statistical data to be described are based on ninety-four obese persons who were overweight 20 per cent or more. The ideal weights were obtained from the height-weight tables furnished by Joslin.¹⁶

We classified our subjects into four groups:

Group I was composed of fifty-three subjects who showed so-called uncomplicated (frank, exogenous) obesity; that is, though distinctly overweight, they showed none of the stigmas of endocrine dysfunction and gave no history or clinical evidence of nephritis, hypertension, diabetes mellitus or arteriosclerosis.

Group II was composed of twenty-five subjects. In these, the obesity was complicated by what may be termed metabolic disorders, namely, essential hypertension, arteriosclerosis and diabetes mellitus. In this class were included all subjects showing a definitely diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance curve, even though signs and symptoms of diabetes mellitus were lacking (the prediabetic state).

Group III was composed of eleven patients in whom obesity was complicated by arthritic manifestations (rheumatoid arthritis and osteo-

14. Blix, G.: Studies on Diabetic Lipemia, *Acta med. Scandinav.* **64**:142, 1926.

15. Rony, H. R., and Levy, A. J.: Studies on Fat Metabolism: I. Fat Tolerance in Obesity. A Preliminary Study, *J. Lab. & Clin. Med.* **15**:221, 1929.

16. Joslin, E. P.: *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1928, p. 967.

arthritis). We deemed it advisable to place these subjects in a separate group, since a study of their plasma cholesterol values showed rather odd results.

Group IV was composed of five patients in whom obesity was complicated (or caused) by definite endocrine dysfunctions (in this series, ovary, thyroid and pituitary dysfunction). Table 1 gives the distribution of the ninety-four cases according to the sex, age and the various groups as previously outlined according to the percentage of overweight.

It is necessary to determine the limits of normality for the cholesterol content of the blood. Rothschild and Wilensky¹⁷ and Weidman and Sunderman¹⁸ reviewed the cholesterol values arrived at by earlier

TABLE 1.—*Distribution (Sex, Age and Groups) According to the Percentage of Overweight in Ninety-Four Cases of Complicated and Uncomplicated Obesity*

Overweight, per Cent	Sex		Average Age, Years (Both Sexes)	Number of Cases of Obesity				Total
	Male	Female		Uncom- plicated	Compli- cated by Metabolic Diseases	Compli- cated by Arthritis	Compli- cated by Endocrine Diseases	
20-30	2	18	44.5	10	6	4	..	20
30-40	..	20	40.6	9	8	3	..	20
40-50	1	15	38.7	10	4	2	..	16
50-60	..	12	33.9	9	..	2	1	12
60-70	1	13	38.7	7	4	..	3	14
70-80	..	5	38.6	3	1	..	1	5
80-90	..	3	37.3	3	3
90-100
100+	..	4	35.0	2	2	4
Total	4	90	53	25	11	5	94

observations. The results obtained with the newer methods (the method of Bloor, Pelkan and Allen¹⁹ and recent modifications) were uniformly higher than those obtained with the older procedures. Bloor²⁰ found that the average cholesterol content of the blood for normal men is 210 mg., and for normal women, 230 mg., but Gorham and Myers²¹

17. Rothschild, M. A., and Wilensky, A. O.: Studies in Cholelithiasis: I. The Disturbances of the Cholesterol Metabolism as a Factor in Gall-Stone Formation, *Am. J. M. Sc.* **156**:239, 1918.

18. Weidman, F. D., and Sunderman, F. W.: Hypercholesterolemia: I. The Normal Blood Cholesterol Figures for Man and for the Lower Animals, *Arch. Derm. & Syph.* **12**:679 (Nov.) 1925.

19. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52**: 191, 1922.

20. Bloor, W. R.: The Distribution of the Lipoids ("Fat") in Human Blood, *J. Biol. Chem.* **25**:577, 1916.

21. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, *Arch. Int. Med.* **20**:599 (Oct.) 1917.

entertained the belief that these figures are too high, and that values ranging between 160 and 170 mg. are more nearly correct. The latter figures are close to the normal values for blood cholesterol accepted by Rabinowitch.²² Hunt,²³ however, gave the upper limit of normal as 230 mg. According to the modified Bloor method employed in this laboratory over a period of almost three years (method of Sackett²⁴), we are inclined to accept the higher values for normality. In fact, we have observed normal fasting subjects with values for plasma cholesterol distinctly above 230 mg. but rarely higher than 250 mg. In our hands, Sackett's method²⁴ modified by the temperature control procedure used in this laboratory²⁵ (the method used in this investigation) leads us to believe that the range of plasma cholesterol in normal subjects lies between 160 and 230 mg.; values from 230 to 250 mg. are only suggestive of hypercholesteremia; figures above 250 mg. are considered to be definitely elevated (hypercholesteremia), and those below 160 mg. to be distinctly below the normal level (hypocholesteremia). We have expressed this view elsewhere.²⁶

The standard deviation as determined for each group was calculated from the formula

$$\mu = \sqrt{\frac{\Sigma(d^2)}{n}}$$

$\Sigma(d^2)$ represents the summation of the squares of the individual deviations from the mean, and n , the number of determinations.

RESULTS

Table 2 shows the results obtained in fifty-three subjects with uncomplicated obesity. The cases are arranged according to the increasing percentage of overweight; the associated clinical conditions considered as materially without influence on the cholesterol content of the plasma are indicated.

In thirty-five cases (66 per cent), the plasma cholesterol was within normal limits; twelve patients (23 per cent) showed hypocholesteremia

22. Rabinowitch, I. M.: The Cholesterol Content of the Blood Plasma in Diabetes Mellitus, *Arch. Int. Med.* **43**:363 (March) 1929; Observations on the Significance of the Cholesterol Content of the Blood Plasma in Diabetes Mellitus, *Canad. M. A. J.* **28**:162, 1933.

23. Hunt, H. M.: Cholesterol in the Blood of Diabetics Treated at the New England Deaconess Hospital, *New England J. Med.* **201**:659, 1929.

24. Sackett, G. E.: Modification of Bloor's Method for Determination of Cholesterol in Whole Blood or Blood Serum, *J. Biol. Chem.* **64**:203, 1925.

25. Mirsky, I. A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, *J. Lab. & Clin. Med.* **18**:304, 1932.

26. Ashe, B. I., and Bruger, M.: The Cholesterol Content of the Plasma in Chronic Nephritis and Retention Uremia, *Am. J. M. Sc.* **186**:670, 1933.

TABLE 2.—*Cholesterol Content of the Plasma in Fifty-Three Cases of Uncomplicated Obesity**

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Over-weight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
1	38	F	162	134	20.9	219	
2	48	F	164	133	23.3	229	Early myocardial insufficiency
3	35	F	163	131	24.4	193	Chronic salpingitis; ovarian cyst
4	29	M	190	152	25.0	207	
5	39	F	164	131	25.1	214	
6	34	F	181	144	25.7	174	
7	30	F	160	127	26.0	201	Chronic cervicitis; rectal ulcers
8	40	F	168	133	26.3	194	
9	63	M	177	140	26.4	276	Paroxysmal tachycardia
10	49	F	172	135	27.4	233	Varicose veins; atrophic rhinitis; chronic otitis media; furunculosis (face)
11	25	F	150	122	30.3	242	
12	32	F	160	123	30.9	176	
13	22	F	158	119	32.8	136	Subcoccygeal fistula
14	54	F	194	146	32.9	202	
15	29	F	164	123	33.3	168	
16	44	F	182	136	33.3	262	Varicose veins
17	36	F	181	135	34.0	327	
18	28	F	191	139	37.4	136	Chronic cholecystitis
19	52	F	189	137	38.0	192	
20	51	F	187	133	40.6	172	
21	43	F	211	150	40.6	149	Endometritis; chronic salpingitis; varicose veins
22	35	F	183	128	43.0	216	
23	23	F	172	120	43.3	179	
24	37	F	195	136	43.4	226	Varicose veins
25	31	F	173	119	45.3	147	Chronic cystitis
26	41	M	265	181	46.4	147	
27	38	F	197	133	48.1	192	Functional amenorrhea
28	42	F	203	136	49.3	154	
29	42	F	187	125	49.6	207	Varicose veins
30	33	F	203	133	52.6	268	
31	39	F	218	141	54.6	169	Uterine fibroid
32	34	F	231	148	56.0	216	Varicose veins
33	23	F	203	130	56.2	162	
34	32	F	197	125	57.6	136	
35	40	F	197	125	57.6	180	
36	25	F	197	124	58.8	119	Chronic cystitis
37	25	F	216	136	58.8	183	Rheumatic heart disease
38	25	F	209	131	59.5	206	Rheumatic heart disease; mitral stenosis
39	35	F	216	135	60.0	160	Varicose veins
40	55	F	223	139	60.4	255	
41	32	F	193	120	60.8	194	
42	39	F	220	136	61.8	158	Varicose veins; ventral hernia
43	36	F	195	119	63.9	133	Hemorrhoids
44	20	F	213	128	66.4	127	
45	36	F	224	133	68.4	148	Chronic endocervicitis
46	27	F	205	119	72.3	259	
47	47	F	241	138	74.6	183	
48	39	F	233	133	76.0	219	Traumatic periostitis
49	30	F	224	124	80.7	214	
50	42	F	289	159	81.7	189	
51	40	F	254	139	82.7	236	
52	35	F	270	132	102.2	193	
53	21	F	292	141	107.0	186	Vaginitis; cervicitis
Average.....						194 ± 43 mg. of cholesterol per 100 cc. plasma	

* The term uncomplicated obesity is used in this study to denote the absence of metabolic, arthritic and endocrine disturbances.

(below 160 mg.), and six (11 per cent), definite hypercholesteremia (above 250 mg.). The highest cholesterol value observed in this group was 327 mg. (case 17); the lowest, 119 mg. (case 36). It is interesting to note the normal or low plasma cholesterol often observed in the

TABLE 3.—*Cholesterol Content of the Plasma in Twenty-Five Cases of Obesity Complicated by Metabolic Diseases (Diabetes Mellitus, Including the Prediabetic State; Essential Hypertension, and Arteriosclerosis)*

Case	Age	Sex	Weight, lbs.	Ideal Weight, lbs.	Over-weight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
54	50	F	165	136	21.3	177	Essential hypertension; cystocele; cardiac asthma
55	45	F	170	136	25.0	280	Essential hypertension; chronic myocarditis
56	56	F	192	150	28.0	326	Essential hypertension; varicose veins
57	51	F	190	148	28.4	213	Essential hypertension; infestation by worms (<i>T. saginata</i>)
58	58	F	181	142	29.6	192	Essential hypertension; myofibro-sitis
59	37	F	187	141	29.9	229	Essential hypertension; diabetic type of dextrose tolerance curve
60	45	F	182	139	30.9	247	Essential hypertension; diabetic type of dextrose tolerance curve; coronary sclerosis; chronic myocarditis
61	46	F	179	136	31.6	278	Diabetes mellitus; coronary sclerosis; sinusitis
62	41	F	194	144	34.7	217	Essential hypertension; cystocele; rectocele
63	43	F	177	134	35.1	296	Diabetic type of dextrose tolerance curve; chronic cystitis
64	40	F	168	124	35.5	260	Diabetic type of dextrose tolerance curve
65	54	F	161	120	36.7	205	Diabetic type of dextrose tolerance curve; syphilis; chronic bronchitis
66	42	F	168	122	37.7	348	Diabetes mellitus
67	48	F	194	140	38.6	221	Essential hypertension
68	55	F	214	151	41.6	210	Diabetes mellitus; cervical polyp
69	32	F	178	125	42.4	245	Diabetic type of dextrose tolerance curve; endocervicitis
70	53	F	202	141	43.2	212	Diabetes mellitus; interdigital blastomycosis
71	35	F	188	128	46.7	278	Essential hypertension
72	39	M	208	145	64.1	153	Essential hypertension
73	50	F	204	142	64.1	270	Diabetic type of dextrose tolerance curve
74	42	F	225	136	65.4	229	Diabetic type of dextrose tolerance curve
75	59	F	241	144	68.5	254	Arteriosclerosis; cystocele
76	48	F	225	132	70.5	178	Essential hypertension; myocardial insufficiency; chronic endocervicitis
77	42	F	298	134	122.3	181	Essential hypertension; menorrhagia
78	42	F	330	145	128.0	259	Diabetic type of dextrose tolerance curve; varicose veins
Average.....						238 ± 16 mg. of cholesterol per 100 cc. plasma	

markedly obese patients (cases 39, 41 to 45, 47 to 50, 52 and 53). The mean cholesterol for the group was 194 ± 43 mg.

Table 3 gives the results obtained in twenty-five subjects in whom essential hypertension, diabetes mellitus or arteriosclerosis was associated with (or resulted from) the obesity. In this group are included

all cases in which the patients showed a diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance test (these are the prediabetic patients).

In thirteen cases of obesity complicated by essential hypertension, three patients showed a definitely elevated plasma cholesterol (cases 55, 56 and 71); in four cases associated with diabetes mellitus, two patients had hypercholesteremia (cases 61 and 66); in seven prediabetic patients, four showed an elevated cholesterol (cases 63, 64, 73 and 78); in one case of obesity associated with arteriosclerosis there was moderate hypercholesteremia (case 75). In the remaining cases, the plasma cholesterol either was only moderately elevated (according to our standards of

TABLE 4.—*Cholesterol Content of the Plasma in Eleven Cases of Obesity Complicated by Arthritis*

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Over-weight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
79	60	F	164	135	20.0	180	Osteo-arthritis; mild endocervicitis
80	47	F	175	143	22.4	274	Osteo-arthritis; cystocele; rectocele
81	34	F	144	114	26.3	170	Gonococcal arthritis; pruritus vulvae; mild endocervicitis
82	46	F	183	143	27.9	178	Osteo-arthritis
83	45	F	173	132	31.1	274	Osteo-arthritis; pruritus vulvae
84	50	F	197	144	36.8	168	Rheumatoid arthritis; cystocele; endocervicitis; parametritis
85	57	F	187	134	39.6	229	Rheumatoid arthritis
86	28	F	186	130	43.0	222	Rheumatoid arthritis; chronic endocarditis; mitral regurgitation
87	34	F	187	130	43.0	227	Osteo-arthritis
88	55	F	218	143	52.5	441	Osteo-arthritis
89	50	F	220	144	52.7	305	Osteo-arthritis; varicose veins
Average.....						243 \pm 77 mg. of cholesterol per 100 cc. plasma	

normality) or indicated a high normal; rarely was hypocholesteremia observed. The mean cholesterol for this group was 238 ± 46 mg.

It should be mentioned here that dextrose tolerance tests were not carried out in all of the ninety-four cases reported. In view of the results obtained in the prediabetic patients, it seems fair to postulate that of the six cases in the uncomplicated group showing hypercholesteremia, some might have shown a diminished tolerance for carbohydrate had the test been carried out and would therefore correctly belong in the former group.

Table 4 indicates the results obtained in eleven cases of obesity associated with either rheumatoid or gonococcal arthritis, or with osteo-arthritis. It is interesting to note that only the moderately obese suffer from arthritis; the percentage of overweight in the eleven cases ranged from 20 to 53.

The plasma cholesterol showed marked differences in individual cases; in case 84 the cholesterol was 168 mg. and in case 88, 441 mg.

Because of these wide variations, it was considered advisable to place the two subjects in a separate group. The probable significance of these results will be considered later. The mean cholesterol for the group was 243 ± 77 mg. The high standard deviation is indicative of the wide variations encountered.

Table 5 shows the results obtained in five cases of obesity complicated (or caused) by endocrine disturbances.

The three obese subjects with hypo-ovarian dysfunction had a normal plasma cholesterol (cases 90, 92 and 94); in one case associated with hypothyroidism, hypercholesteremia was present (case 91); in another with acromegaly there was also a distinctly elevated plasma cholesterol (case 93). The mean cholesterol for the group was 224 ± 47 mg.

TABLE 5.—*Cholesterol Content of the Plasma in Five Cases of Obesity Complicated by Endocrine Diseases*

Case	Age	Sex	Weight, Lbs.	Ideal Weight, Lbs.	Over-weight, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Associated Clinical Conditions
90	26	F	190	122	55.7	218	Hypo-ovarian dysfunction; amenorrhea
91	20	F	205	124	65.3	261	Hypothyroidism
92	27	F	227	137	65.7	161	Hypo-ovarian dysfunction
93	42	F	280	169	65.7	289	Acromegaly
94	32	F	222	128	73.4	186	Hypo-ovarian dysfunction
Average.....						221 ± 47 mg. of cholesterol per 100 cc. plasma	

COMMENT

A detailed discussion of the causal relationship between obesity, on the one hand, and essential hypertension, diabetes mellitus and arteriosclerosis, on the other, is beyond the scope of this paper. Suffice it to say that clinicians have stressed such a relationship for many years; health institutes and life insurance companies have published pertinent statistics which apparently prove that these degenerative diseases occur with great frequency in persons who are overweight.

We are impressed by the fact that degenerative diseases, in contrast to the purely inflammatory or productive types, are usually associated with an increased blood cholesterol. Cell degeneration rather than cell destruction is accompanied by hypercholesteremia, e. g., in nephrosis, arteriosclerosis and similar conditions. The cellular disintegration that occurs in inflammatory processes and in the cachexias resulting from a variety of morbid lesions is generally associated with a moderate to a marked diminution of the cholesterol content of the blood.

Our results have shown that in obese subjects in whom obvious degenerative processes were lacking, the cholesterol content of the

plasma was within normal limits. When essential hypertension, diabetes mellitus or arteriosclerosis supervened, the blood cholesterol increased in many instances; it seems correct to conclude, therefore, that this hypercholesteremia represents the effect rather than the cause of the onset of the degenerative changes in obese subjects.

In a recent critical review on the subject of diet and blood lipoids, Bloor²⁷ stated that the continuous feeding of diets high in fat, on the one hand, and low in fat, on the other hand, produced definite changes in the level of the plasma cholesterol of dogs and rabbits. The cholesterol was always higher with a diet high in fats than with one low in fats; the difference was not so great in the dog, but it was marked in the rabbit. The fifty-three cases of uncomplicated obesity discussed in the preceding paragraphs may be considered as a representative group in which the obese state was probably due to the increased consumption of fat and of carbohydrate over a period of years. The cholesterol content of the plasma in these subjects, however, was usually within normal limits; in many instances the cholesterol was below the accepted standard for normality. Apparently, the continuous consumption of a diet high in fats over a period of months or years was even less effective in augmenting the blood cholesterol in human beings than in dogs.

A number of investigators have recorded the increased blood cholesterol in patients with diabetes mellitus (Joslin, Bloor and Gray,²⁸ Myers,²⁹ Malerba,³⁰ Labbé and Heitz,³ Gray,¹⁰ Rabinowitch,²² White and Hunt⁸ and others). In 1929 and 1933, Rabinowitch²² stressed the prognostic significance of cholesterol determinations in diabetic patients. In eleven of our subjects in whom the obesity was complicated by diabetes mellitus or in whom a diminished tolerance for carbohydrate was evident from the dextrose tolerance test, six showed hypercholesteremia; the remaining five gave normal values.

Pribram and Klein,³¹ Westphal,³² and Waldorp⁶ reported an augmented blood cholesterol in patients with essential hypertension. Weil,

27. Bloor, W. R.: Diet and the Blood Lipoids, *J. Biol. Chem.* **95**:663, 1932.

28. Joslin, E. P.; Bloor, W. R., and Gray, H.: The Blood Lipoids in Diabetes, *J. A. M. A.* **69**:375 (Aug. 4) 1917.

29. Myers, V. C.: Chemical Changes in the Blood in Disease: VI. Cholesterol, *J. Lab. & Clin. Med.* **5**:776, 1919-1920.

30. Malerba, G. L.: Il tasso colesterinico del siero di sangue in varie forme morbose, *Riforma med.* **37**:602, 1921.

31. Pribram, H., and Klein, O.: Ueber den Cholesteringehalt des Blutserum bei arteriosklerotischem Hochdruck, *Med. Klin.* **20**:572, 1924.

32. Westphal, K.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes: IV. Cholesterin als tonogene Substanz der genuinen Hypertension im Zusammenspiel mit anderen Entstehungsbedingungen. *Ztschr. f. klin. Med.* **101**:584, 1925.

Guillaumin and Abricosoff⁴ believed that there was a direct relationship between the height of the arterial tension and the degree of hypercholesteremia. In thirteen of our patients in whom the obese state was associated with hypertension, only three showed hypercholesteremia; the remaining ten gave high normal values, but the cholesterol was rarely low. The incidence of an increased blood cholesterol in hypertensive subjects found in our group of thirteen cases (23 per cent) was distinctly lower than that given by Westphal³² (71 per cent). The maximum normal cholesterol adopted by us (250 mg.) is comparatively high according to the standards used by other investigators; this probably accounts for the difference in the incidence in the two series.

The blood cholesterol is reputed to be elevated in arteriosclerosis (Myers²⁰). This hypercholesteremia forms the basis of Aschoff's³³ theory of the pathogenesis of arteriosclerosis. In one case of obesity complicated by arteriosclerosis studied in this series there was a moderately increased plasma cholesterol.

Gorham and Myers²¹ studied five cases of arthritis and found the cholesterol content of the blood to be within normal limits. Pemberton and Robertson³⁴ reported fourteen cases and found the cholesterol to be subnormal; they felt that their findings supported the infectious theory of arthritis. In our eleven cases, the plasma cholesterol varied considerably in individual subjects; in general it may be stated (though this is by no means true for all of the cases) that the subjects with osteo-arthritis showed a higher blood cholesterol than those with infectious (rheumatoid or gonococcal) arthritis. Our series, however, is too small to permit us to make definite statements. The theoretical considerations outlined at the beginning of this discussion are apparently further supported by the findings in this group; the chronic arthropathy designated as osteo-arthritis (hypertrophic arthritis) is primarily a degenerative disease³⁵ and is more often associated, though not invariably, with a higher blood cholesterol than is the purely infectious or inflammatory type (rheumatoid or gonococcal arthritis). This phase of the subject deserves further investigation, the results of which should prove interesting.

Muller³⁶ recently reviewed the literature on the relation between the organs of internal secretion and cholesterol metabolism. The

33. Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924, pp. 142 and 143.

34. Pemberton, R., and Robertson, J. W.: *Studies on Arthritis in the Army Based on 400 Cases: I. Preamble and Statistical Analysis*, *Arch. Int. Med.* **25**: 231 (March) 1920.

35. Cecil, R. L.: *A Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1930, p. 1254.

36. Muller, G. L.: *The Cholesterol Metabolism in Health and in Anemia*, *Medicine* **9**:119, 1930.

increased cholesterol content of the blood in hypothyroidism has been observed frequently both clinically and experimentally. A single case of obesity associated with hypothyroidism studied in this series showed a moderately elevated plasma cholesterol. In our three cases of obesity complicated by hypo-ovarianism there were normal cholesterol values; Blix,¹⁴ however, was of the opinion that hypo-ovarian dysfunction was accompanied by hyperlipoidemia. In one case of acromegaly in this group there was hypercholesteremia; in the case reported by Gorham and Myers²¹ the blood cholesterol was within normal limits.

SUMMARY

The plasma cholesterol in fifty-three obese subjects, in whom evidence of metabolic, arthritic or endocrine disturbances was lacking, was usually within normal limits.

The advent of diabetes mellitus, essential hypertension or arteriosclerosis in eighteen obese persons was associated in many instances with an augmented cholesterol content of the plasma. Four of seven overweight subjects who demonstrated a diminished tolerance to ingested carbohydrate as determined by the dextrose tolerance test, even though signs and symptoms of diabetes mellitus were lacking, showed an increased plasma cholesterol.

In four obese persons with infectious (rheumatoid or gonococcal) arthritis, the plasma cholesterol was usually within the normal limits; in seven cases with degenerative hypertrophic arthritis or osteo-arthritis, the cholesterol was often significantly elevated.

CONCLUSIONS

A high caloric diet, presumably high in carbohydrates and fats, which results in obesity is not accompanied by a rise of the plasma cholesterol in human beings.

The development of degenerative diseases (hypertension, diabetes, arthritis and arteriosclerosis) in the obese is as a rule followed, and not preceded, by hypercholesteremia. Therefore, the elevated concentration of the cholesterol in the blood in these degenerative conditions is usually to be regarded as a complication and not in the light of an etiologic factor.

MUSCULAR DYSTROPHY AND ATROPHY

CLINICAL AND BIOCHEMICAL RESULTS FOLLOWING THE ORAL ADMINISTRATION OF AMINO-ACIDS

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One of the most perplexing, and yet one of the most interesting problems encountered in medical practice in general, and in clinical neurology in particular, is constituted by that group of patients who are suffering from some form of muscular atrophy or dystrophy.

Perhaps the first complete descriptions of the various forms of muscular dystrophy and atrophy were presented about the middle of the nineteenth century during the time of Charcot¹ and his colleagues. Since that time numerous investigators have studied the problem in its various phases, and much information has been added toward a thorough comprehension of the characteristic clinical syndromes, with their associated pathologic lesions. Various theories as to the etiology of the condition have been presented and many therapeutic measures have been proposed, none of which have withstood the test of time.

The results of many studies have shown that in cases of muscular dystrophy the creatine metabolism of the muscles becomes deranged. In 1909, Levene and Kristeller² showed that the feeding of protein resulted in increased excretion of creatine in cases of muscular dystrophy. This observation was later confirmed by several investigators, chiefly Gibson and Martin³ and Buell.⁴ However, progress in this field was retarded

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A preliminary report of these studies was made at the meeting of the American Society of Biological Chemists held at Cincinnati in April, 1933.

1. Charcot, J. M.: *Lectures on Diseases of the Nervous System*, Paris, 1868; English translation, London, New Sydenham Society, 1877.

2. Levene, P. A., and Kristeller, L.: *Factors Regulating the Creatinin Output in Man*, *Am. J. Physiol.* **24**:45, 1909.

3. Gibson, R. B., and Martin, F. T.: *Creatine Formation in a Case of Progressive Pseudohypertrophic Muscular Dystrophy*, *J. Biol. Chem.* **49**:319, 1921.

4. Gibson, R. B.; Martin, F. T., and Buell, M. V. R.: *A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies*, *Arch. Int. Med.* **29**:82 (Jan.) 1922.

for many years, because of the general belief that creatine in the muscles was a product of endogenous metabolism and that it could not be increased by the feeding of proteins or amino-acids. It seemed useless, therefore, to try to increase the formation of creatine by means of diet alone.

A recent review of the literature,⁵ however, shows that there is evidence of the formation of creatine from such amino-acids as cystine, arginine and histidine. Brand, Harris, Sandberg and Ringer⁶ were the first to show that the feeding of glycine caused an increase of 40 per cent in the excretion of creatine. Since there are about twenty amino-acids in the protein molecule, it is unlikely that one particular amino-acid could form creatine; it would seem, rather, that this might be a property of any one or all of them, as was definitely shown in the extensive studies of Barnes and one of us (H. H. B.⁵) in 1931. Proteins and amino-acids, when fed in sufficient amounts daily, increased the creatine content of muscles in young rats, and the excretion of creatinine in adult rats and human subjects.

It is well known from the work of many investigators that the patient who is suffering from muscular dystrophy is unable to retain creatine in his muscles. If this substance is ingested, most of it is excreted in the urine, making the patient practically "diabetic" as regards creatine. Recent work, which will be discussed later, has proved that the patient can form large amounts of creatine when certain amino-acids are fed in sufficient quantities. For a few weeks after such feeding there is an increased creatinuria, which gradually subsides, the creatine being retained in the muscles. At this time, clinical improvement and an increase in muscular function are noted.

It is also well known that a close relationship exists between creatine and carbohydrate metabolism. For instance, the creatinuria of starvation can be abolished by feeding carbohydrates. In 1925, Moren⁷ and others noted a distinct, although not marked, clinical improvement in patients with muscular dystrophy to whom glycogen or sugar had been fed.

The first definite therapeutic effects of feeding glycine to patients suffering from muscular dystrophies were reported in 1932 by Milhorat, Techner and Thomas⁸ in Germany.

5. Beard, H. H., and Barnes, B. O.: The Influence of Feeding Proteins, Amino Acids and Related Substances upon Creatine-Creatinine Metabolism, *J. Biol. Chem.* **94**:49, 1931.

6. Brand, E.; Harris, M. M.; Sandberg, M., and Ringer, A. I.: Studies on the Origin of Creatine, *Proc. Internat. Physiol. Congress*, 1929, p. 36.

7. Moren, J. J.: Treatment of Muscular Dystrophies, *Kentucky M. J.* **23**:528, 1925.

8. Milhorat, A. T.; Techner, F., and Thomas, K.: Significance of Creatine in Progressive Muscular Dystrophy, and Treatment of This Disease with Glycine, *Proc. Soc. Exper. Biol. & Med.* **29**:609, 1932.

The following excerpt from their paper is of interest:

After a period of some weeks (depending upon how advanced the case is) the creatinuria begins to decrease, despite the continuance of glycine, until it falls to the former control level. While these changes in metabolism are taking place the patient improves in a remarkable manner. The first symptom manifested in half our patients was a curious feeling in the muscles which they describe as a "crawling, rumbling" sensation, which in one case was so severe that sleep was definitely interfered with. The next change in the clinical course is the disappearance of the fatigue that frequently constitutes a prominent and distressing symptom in this disease. The muscles that had previously felt tired and heavy now feel refreshed and lighter, and the patients often desire to make muscular movements they have not been able to make for a long time. Gradually, the function of certain muscle groups so improves that activities can be performed that had been impossible for years (climbing stairs, arising from the floor unaided, riding a bicycle). The degree of improvement differs not only in different patients, but in different muscles in the same patient. The time required for such improvement varies widely. One patient showed a remarkable improvement in three weeks; in another no definite increase in muscle function could be demonstrated at the end of nine weeks, although there was much subjective improvement.

These interesting results have stimulated several clinicians to use glycine, with and without ephedrine, in the treatment of muscular dystrophy and myasthenia gravis. In September, 1932, Boothby⁹ of the Mayo Clinic, reported considerable success with glycine therapy in three cases of myasthenia gravis. In December of the same year, Boothby¹⁰ reported six additional cases, making a total of nine of his own cases of myasthenia gravis in which this treatment was employed. Remen¹¹ reported remarkable improvement from glycine therapy in one case of myasthenia gravis. Schmitt,¹² Van Dalsem¹² and Trubek¹² also reported success in the treatment of myasthenia gravis with glycine or a combination of glycine and ephedrine. Reese¹³ reported success with glycine in two cases of muscular dystrophy, the type of which was not stated, and in three cases of myasthenia gravis. Taylor¹⁴ used gelatin, which contains about 25 per cent of glycine, in a case of myasthenia gravis with no effect, whereas when gelatin was administered in combination with ephedrine a remarkable clinical improvement was noticeable.

9. Boothby, W. M.: Myasthenia Gravis: A Preliminary Report on the Effect of Treatment with Glycine, *Proc. Staff Meet., Mayo Clin.* **7**:557 (Sept. 28) 1932.

10. Boothby, W. M.: Myasthenia Gravis: Second Report on the Effect of Treatment with Glycine, *Proc. Staff Meet., Mayo Clin.* **7**:737 (Dec. 28) 1932.

11. Remen, L.: Zur Pathogenese und Therapie der Myasthenia gravis pseudo-paralytica, *Deutsche Ztschr. f. Nervenhe.* **128**:66, 1932; cited by Boothby.¹⁰

12. Cited by Boothby.¹⁰

13. Reese, H. H.: Personal communication to one of us (H. H. B.).

14. Taylor, R.: A New Treatment for Myasthenia Gravis, *South. Med. & Surg.* **94**:790, 1932.

Milhorat¹⁵ recently reported distinct clinical improvement in fourteen cases of progressive muscular dystrophy treated with glycine.¹⁶ He found that this substance caused a decided increase in creatinuria, which was further enhanced by the addition of phosphates to the diet. Milhorat has shown histologically that after amino-acid therapy the muscles either show complete atrophy or present the picture of normal muscle fibers. He also proposed the older theory of abiotrophy, a hereditary disturbance manifesting itself by a loss of potentiality of the motor system, so that the stress of advancing years cannot be withstood. Our histologic studies have confirmed these observations. It appears that those muscle fibers in which the nuclei have begun to show pyknosis do not return to normal after amino-acid therapy is begun, but progress to complete atrophy with resultant fibrosis. However, those muscles in which the fibers have not reached this stage of degeneration present a normal histologic picture after therapy has been continued for a sufficient length of time.

Recently, we¹⁷ presented a biochemical study of creatine-creatinine metabolism in various muscular conditions, namely, progressive muscular dystrophy, progressive spinomuscular atrophy, myasthenia from disuse and amyotrophic lateral sclerosis, wherein we especially noted that the creatinuria was greater in the cases of muscular dystrophy than in those cases in which atrophy was associated with lesions of the spinal cord. At the same time, Chanutin, Butt and Royster¹⁸ reported five cases of pseudohypertrophic muscular dystrophy in one family. One boy was treated with glycine with remarkable results. Two brothers who were treated with creatine showed improvement for one month, and then became progressively worse.

Brand and Harris¹⁹ are the only investigators who have so far reported unsatisfactory results from amino-acid therapy in cases of muscular dystrophy. These workers kept their patients on a meat-free

15. Milhorat, A. T.: Ueber die Behandlung der progressiven Muskeldystrophie und ähnlicher Muskelerkrankungen mit Glykokoll, *Deutsche Arch. f. klin. Med.* **174**:487, 1933.

16. It might be well to mention here a note made by Quick (J. A. M. A. **99**:57 [July 2] 1932) who, citing the work of Milhorat, Techner and Thomas, noted that glycine or glycocoll (amino-acetic acid) should not be confused with the photographic developer which is sold under the trade name of "glycin." This compound is p-hydroxyphenylamino-acetic acid and is distinctly poisonous.

17. Beard, H. H., and Tripoli, C. J.: The Effect of Feeding Amino Acids in Cases of Muscular Dystrophy, *J. Biol. Chem.* **100**:14, 1933.

18. Chanutin, A.; Butt, H. R., and Royster, L. T.: A Study of Progressive Pseudohypertrophic Muscular Dystrophy in Children After the Administration of Glycine and Creatine, *J. Biol. Chem.* **100**:26, 1933.

19. Brand, E., and Harris, M. M.: Further Studies on the Administration of Glycine in Muscular and Neuromuscular Diseases, *J. Biol. Chem.* **100**:20, 1933.

diet low in purine during glycine therapy. We believe this to be an error, since normal protein metabolism must be maintained so that the "excess" amino-acid will be available for creatine formation. Brand and Harris did not observe the "crawling rumbling" sensations which are noted in those patients who respond to this type of therapy. Another fact of importance is that the patients were unable to retain the newly formed creatine in the body, since they continued to excrete this substance for as long as nine months after treatment. The work of these authors, however, has not progressed far enough at this time for definite conclusions to be drawn.

Kostakow and Slauck²⁰ recently reported beneficial results in seven patients with progressive muscular dystrophy treated with glycine, and added a note on its effect in spinal paralysis in children.

Table 1 presents a summary of the cases in which amino-acids are being used at the present time.

We wish to report in this paper our observations in cases of progressive spinomuscular atrophy, progressive muscular dystrophy, psychopathic inferiority complex with loss of muscle tissue from disuse, pseudohypertrophic muscular dystrophy and amyotrophic lateral sclerosis, in all of which amino-acid therapy was used. Our reasons for using glutamic acid in place of glycine in several cases are as follows: (a) According to Needham,²¹ glutamic acid constitutes 16 per cent of the protein in the muscles. (b) We observed in earlier work that glutamic acid is a slightly better creatine former in young rats than glycine. (c) Glycine costs 2.6 cents a gram, while pure glutamic acid can be purchased for 1.2 cents a gram. (d) Glutamic acid is nontoxic, while glycine may be slightly toxic, as was noted when large doses were given to rats.²²

The patients gave excellent cooperation, three of them collecting their own specimens of urine. The creatine-creatinine excretion was studied during a control period of from four to seven days before the administration of the amino-acids was begun. The total nitrogen, total creatinine and total creatine were determined daily in the twenty-four hour

20. Kostakow, S., and Slauck, A.: Glycine Treatment of Progressive Muscular Dystrophy, *Deutsche med. Wchnschr.* **59**:169 (Feb. 3) 1933.

21. Needham, D.: *The Biochemistry of Muscle*, London, Methuen & Co., 1932, p. 96.

22. Sullivan, M. X.; Hess, W. C., and Sebrell, W. H.: Studies on the Biochemistry of Sulphur: XII. Preliminary Studies on the Amino-Acid Toxicity and Amino-Acid Balance, *Pub. Health Rep.* **47**:75 (Jan. 8) 1932. Lillie, R. D.: Histopathologic Changes Produced in Rats by the Addition to the Diet of Various Amino Acids (Glycine, Lysine, Tryptophane, Cystine, Tyrosine and Glutamic Acid, and Glutathione, and of Mixtures of Some of Them), *ibid.* **47**:83 (Jan. 8) 1932.

TABLE 1.—*Summary of Cases in Which Amino-Acids Were Used*

Type of Disease	No. of Cases	Author	Therapy	Increase in Creatinuria	Clinical Results
Progressive muscular dystrophy	3	Milhorat, Techner and Thomas ⁸	Glycine	++	Marked improvement
Pseudohypertrophic muscular dystrophy	3	Milhorat, Techner and Thomas ⁸	Glycine	++	Marked improvement
Amyotrophic lateral sclerosis	1	Milhorat, Techner and Thomas ⁸	Glycine	+	No improvement
Myasthenia gravis	9	Boothby ⁹	Glycine with and without ephedrine	++	Marked improvement
Muscular dystrophy	2	Boothby ⁹	Glycine	++	Slight improvement
Myasthenia gravis	1	Refnen ¹¹	Glycine	Marked improvement
Myasthenia gravis	1	Schmitt ¹²	Glycine and ephedrine	Marked improvement
Myasthenia gravis	1	Van Dalsem ¹²	Glycine and ephedrine	Marked improvement
Myasthenia gravis	1	Trubek ¹²	Glycine	Marked improvement
Muscular dystrophy	2	Reese ¹³	Glycine	Good
Myasthenia gravis	3	Reese ¹³	Glycine	Good
Myasthenia gravis	1	Taylor ¹⁴	Gelatin with ephedrine	Marked improvement
Spinomuscular atrophy	1	Beard and Tripoli ¹⁷	Glycine	+++	Slight improvement
Progressive muscular dystrophy	1	Beard and Tripoli ¹⁷	Glutamic acid	++	Marked improvement
Amyotrophic lateral sclerosis	1	Beard and Tripoli ¹⁷	Glutamic acid	No improvement
Amyotrophic lateral sclerosis	1	Beard and Tripoli ¹⁷	Glutamic acid	++	Improvement for one month, then progressively worse
Psychopathic inferiority complex	1	Beard and Tripoli ¹⁷	Glutamic acid	+	Improvement marked, possibly due partly to physiotherapy
Pseudohypertrophic muscular dystrophy	1	Beard and Tripoli ¹⁷	Glutamic acid and glycine	..	Slight improvement after 2½ months
Progressive pseudohypotrophic muscular dystrophy	1	Chanutin, Butt and Royster ¹⁸	Glycine	+ (?)	Marked improvement
Progressive pseudohypotrophic muscular dystrophy	2	Chanutin, Butt and Royster ¹⁸	Creatine	..	Improvement for one month, then progressively worse
Progressive muscular dystrophy	9	Brand and Harris ¹⁹	Glycine (meat-free, low purine diets)	++	No improvement
Progressive muscular dystrophy	14	Milhorat ¹⁵	Glycine	++	First a rapid and then a slower improvement in the functional capacity of the muscles
Myotonia congenita	1	Milhorat ¹⁵	Glycine	..	Good
Flaccid muscles	1	Milhorat ¹⁵	Glycine	..	Good
Progressive muscular dystrophy	7	Kostakow and Slauck ²⁰	Glycine	++	Good

Total number of cases studied, 69.

Total number of cases clinically improved, 51.

specimen of urine in the case of each patient. At the beginning of the second period (shown by the arrows on the charts) 10 Gm. of glycine dissolved in milk was given to the patient suffering from progressive spinomuscular atrophy, and 10 Gm. of glutamic acid was given to the other five patients. The effect of the ingestion of amino-acid on the excretion of the total nitrogen, total creatinine, preformed creatinine and creatine in the first four cases is shown in figures 1, 4, 5 and 6.

Our studies were planned along several lines: first, to determine the creatine-creatinine metabolism of as many types of cases of muscular dystrophy and atrophy as possible, with particular attention to the effect of amino-acid therapy from both a biochemical and clinical aspect; second, to attempt a classification of the allied dystrophic-atrophic conditions on a pathologic-physiologic basis; third, to endeavor to formulate a basis for prognosis in the various types of cases.

REPORT OF CASES

The clinical data of our cases follow:

CASE 1.—A white man, aged 26, had been suffering from progressive spinomuscular atrophy for nine months. The early symptoms were muscular tremors, with weakness and fatigue on slight exertion, the muscles of the shoulder girdle and upper extremity being particularly affected. Marked asymmetrical body weakness was present, being more noticeable on the left than on the right side. Later, wasting of the interossei and lumbricales muscles of both hands was noted. Complete analyses of the blood and spinal fluid and roentgenologic examination gave negative results. Ten grams of glycine was given daily in milk beginning Dec. 1, 1932. After six weeks of this treatment the patient gained definitely in weight; there was a partial return of muscular strength, with a notable diminution of the tremulous twichings in the left shoulder, but not in the right one. Since that time improvement has ceased.

CASE 2.—A white man, aged 36, had been suffering from progressive muscular dystrophy for twenty-one years. Atrophy began in the muscles of the shoulder girdle, gradually progressing throughout the muscular system of the thorax and abdomen until at the time the patient came under our observation the pelvic girdle was involved to such an extent that a "wobbling gait" resulted. Complete analyses of the blood and spinal fluid and roentgenographic examination gave negative results. All previous therapeutic regimens, including diet, physical therapy and stimulating tonic drugs, resulted in no definite effect on the progress of the disease. Ten grams of glutamic acid was given daily in milk, beginning Dec. 1, 1932. After one month of treatment, definite muscular improvement, both subjective and objective, was noted. There was an increase in weight; the "wobbling gait" disappeared, and the patient was able to walk four miles daily without fatigue. Improvement has been continuous in those muscles in which atrophic changes were taking place, but not in those in which resultant fibrotic changes of long standing had occurred. This finding is in keeping with the observations of Milhorat.¹⁵

Physical examination of the patient five months after the institution of glutamic acid therapy showed continued improvement. The strength of the muscles of the

back was marked. The left rectus abdominis muscle was markedly improved, whereas the right showed only slight improvement. The muscles of the arm and shoulder girdle, particularly those in which atrophic changes were practically complete, showed no evidence of improvement. However, those muscles which were not completely atrophic have regained their function and strength (figs. 2 and 3). The muscles of the leg, as noted, have continued to improve until little or no diminution from the normal in function or anatomy can be determined at the present time.

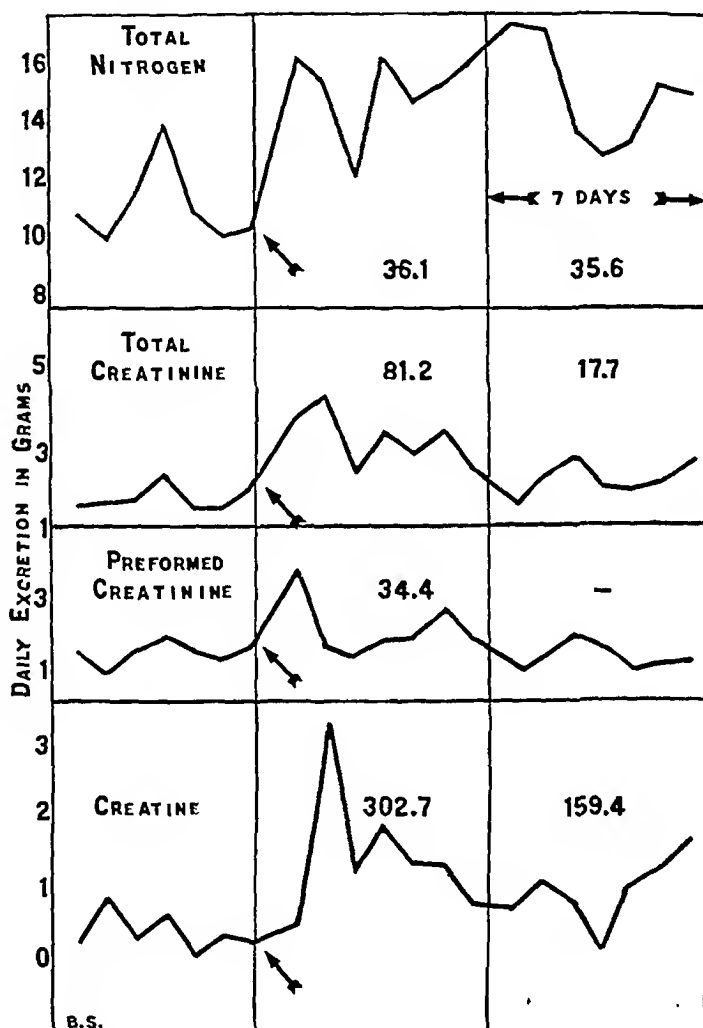


Fig. 1.—Effect of the ingestion of glycine on a patient with neuromuscular atrophy. The first seven days represent the control period. The arrows indicate the point at which 10 Gm. of glycine was given daily in milk to the patient. The figures in the succeeding periods show the average increase in per cent of the different constituents over that of the control period.

CASE 3.—A white woman, aged 31, suffered from a psychopathic inferiority complex of five years' duration, following a disappointment in love. Physical examination revealed marked muscular atrophy of both lower extremities, resulting from a self-imposed, protracted stay in bed. The patient had been unable to walk for some time. Ten grams of glutamic acid was given in milk beginning on

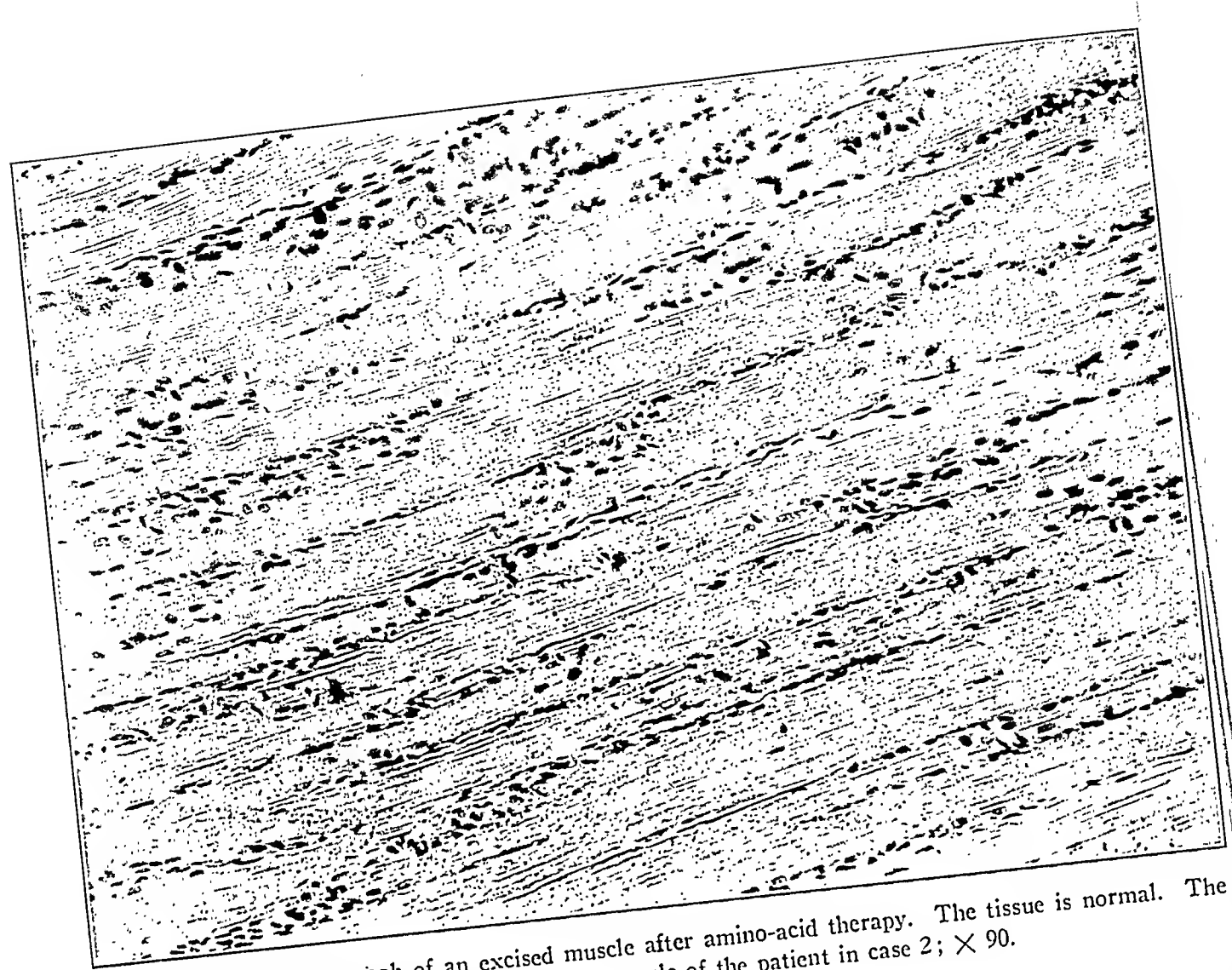


Fig. 2.—Photomicrograph of an excised muscle after amino-acid therapy. The tissue is normal. The specimen was taken from the gluteus maximus muscle of the patient in case 2; $\times 90$.

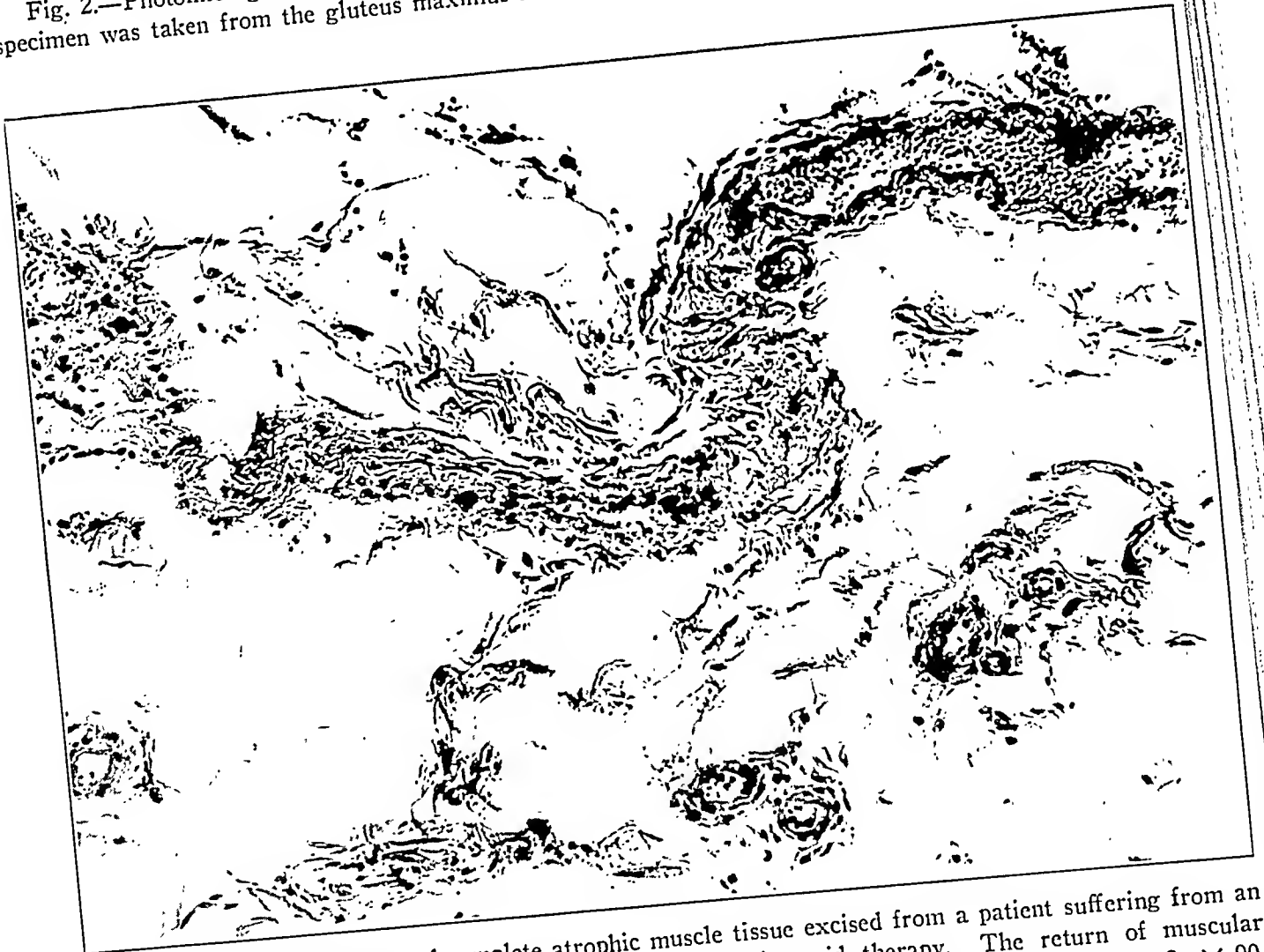


Fig. 3.—Photomicrograph of complete atrophic muscle tissue excised from a patient suffering from an advanced case of progressive muscular dystrophy, after amino-acid therapy. The return of muscular function is impossible. The specimen was taken from the trapezius muscle of the patient in case 2; $\times 90$.

Dec. 13, 1932. General improvement, such as increase in body weight and strength and ability to walk, was noted after a few weeks of treatment. This improvement, however, may have been owing, in part at least, to the hygienic or physical therapy regimens which were simultaneously instituted.

CASE 4.—A white man, aged 26, suffered from amyotrophic lateral sclerosis. In December, 1931, he noticed weakness and wasting in the arms, particularly in the left forearm and hand. The symptoms were progressive until December, 1932, at which time distinct weakness, atrophy and twitching of the muscles of the left shoulder, left side of the chest, arm, forearm and hand were noticeable, the latter

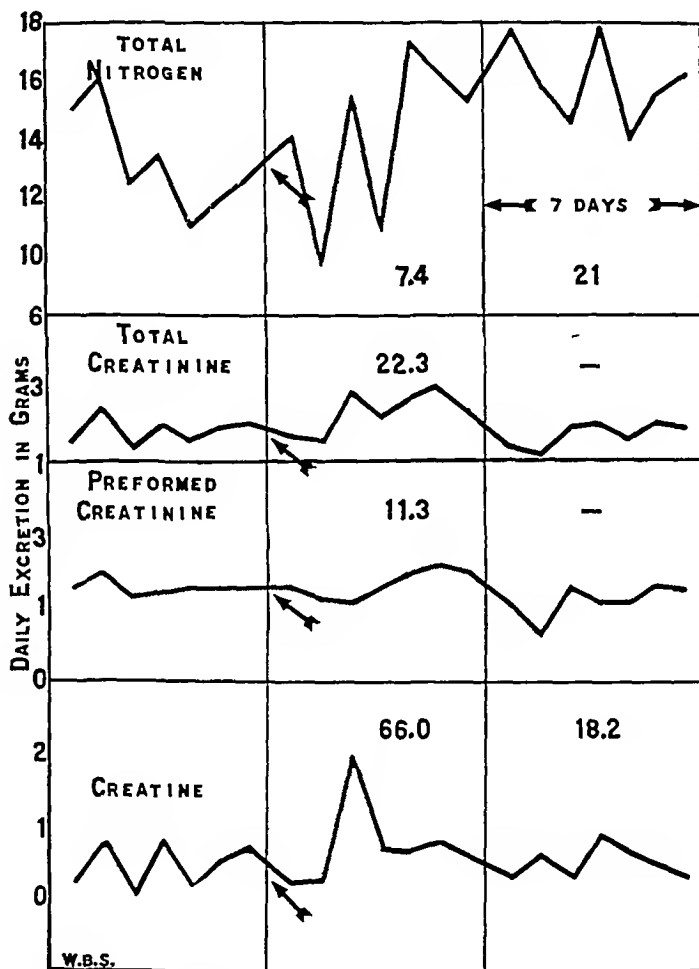


Fig. 4.—Effect of the ingestion of glutamic acid on a patient with progressive muscular dystrophy. The first seven days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the second and third weeks show the average increase in per cent of the different constituents over that of the control period.

progressing until marked atrophy of the interossei and lumbricales muscles was evident. This resulted in a very weak grip in the left hand. The patient was unable to flex the index finger, or facilitate "grouping" of the fingers of the left hand. Twitchings were marked in the left upper extremity and slight in the right upper extremity. The leg showed marked weakness with dysfunction of the anterior tibial group of muscles to the extent that the patient's normal gait was frequently interrupted by stumbling. Slight atrophy of the muscles was also

present. Complete analyses of the blood and spinal fluid and roentgenographic examination gave negative results. After 10 Gm. of glutamic acid in milk had been administered daily for four weeks, the left leg became stronger, and the patient no longer stumbled when walking. The muscle tone of the left arm improved to such an extent that the ability to flex and extend the left forefinger returned. Grouping was also improved in the left hand, but the muscular twitchings became more marked in the right arm. During the past few weeks the patient's progress seems to have ceased, and at the present time his clinical picture is stationary.

CASE 5.—A man, aged 45, was suffering from advanced pseudohypertrophic muscular dystrophy of twenty-three years' duration. The typical anterior curvature

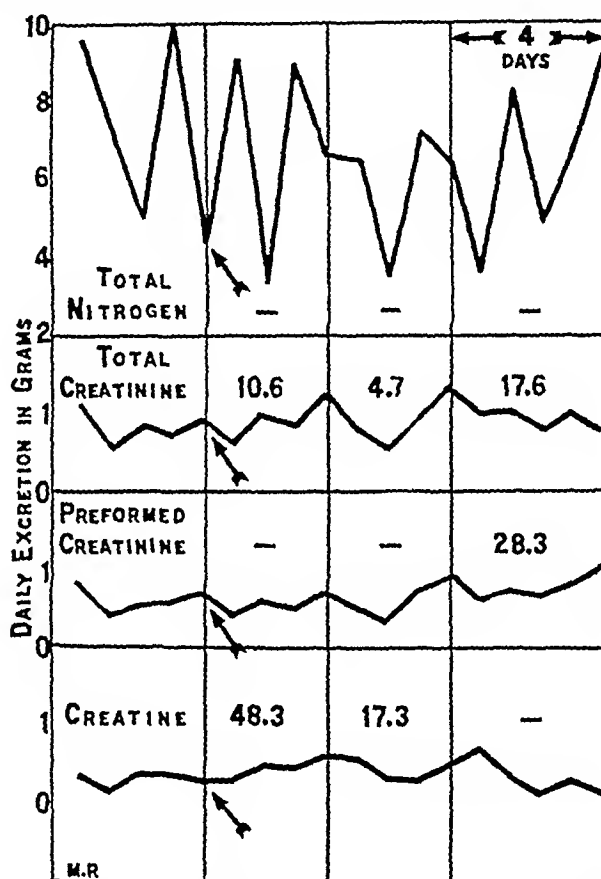


Fig. 5.—Effect of the ingestion of glutamic acid on a patient with a psychopathic inferiority complex. The first four days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the succeeding periods represent the average increase in per cent of the different constituents over that of the control period.

of the lower thoracic and lumbar segments of the spine with marked protuberance of the abdomen had taken place. The condition of the muscles was characteristic of the disease. The patient was unable to dress himself. He was so weak that he was able to assume a standing position only with the help of a support such as his desk, literally "climbing" up by using the muscles of his shoulder and arm. Of late he had begun to notice an increased difficulty in rising caused by weakness of these muscles. On Feb. 16, 1933, 10 Gm. of glutamic acid was administered, and this treatment was continued daily for one month without improvement. Later, glycine was substituted and the dosage increased to 20 Gm.,

administered twice daily. During a period of two and one-half months the patient began to show slight improvement, particularly a marked gain in body weight. Recently, ephedrine was added in an attempt to enhance the therapeutic effect of the amino-acid therapy. We believe that glycine therapy has checked the progress of the disease. Slight improvement, evidenced by a better hand grip and a more stable gait, has occurred, but the duration of therapy has not been sufficient to bring about greater return of function. We expect to see further improvement in this case.

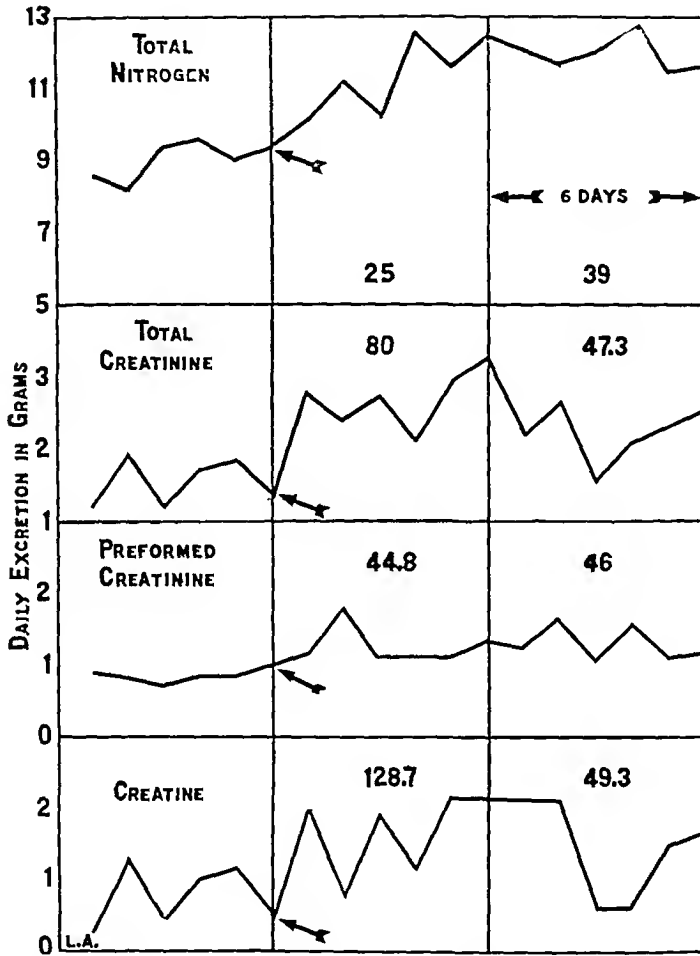


Fig. 6.—Effect of the ingestion of glutamic acid on amyotrophic lateral sclerosis. The first six days represent the control period. The arrows indicate the point at which 10 Gm. of glutamic acid was given daily in milk to the patient. The figures in the succeeding periods represent the average increase in per cent of the different constituents over that of the control period.

CASE 6.—A white woman, aged 61, suffered from amyotrophic lateral sclerosis. She complained of pain in the back, weakness of the knees and dragging of the left foot. The family history was not important. Two years previous to examination the patient fell and has been very weak since that time. She has fallen several times during the past two years. Three weeks prior to examination her condition became steadily worse. She drags her left foot. Her knees are weak, and she is unable to walk alone. Her hands, especially the left, are weak and numb. The positive neurologic findings were: left foot drop; general increase of deep reflexes; positive Babinski and Hoffman sign bilaterally; muscular weakness exhibited in

the grip of the hand and extension of the foot; atrophy of the interossei muscles of the hands. Ten grams of glutamic acid has been administered daily since March 20, 1933. No clinical improvement has been noted up to the present time.

COMMENT

The results shown in figure 7 indicate that both creatine and creatinine may be formed from glycine or glutamic acid administered orally

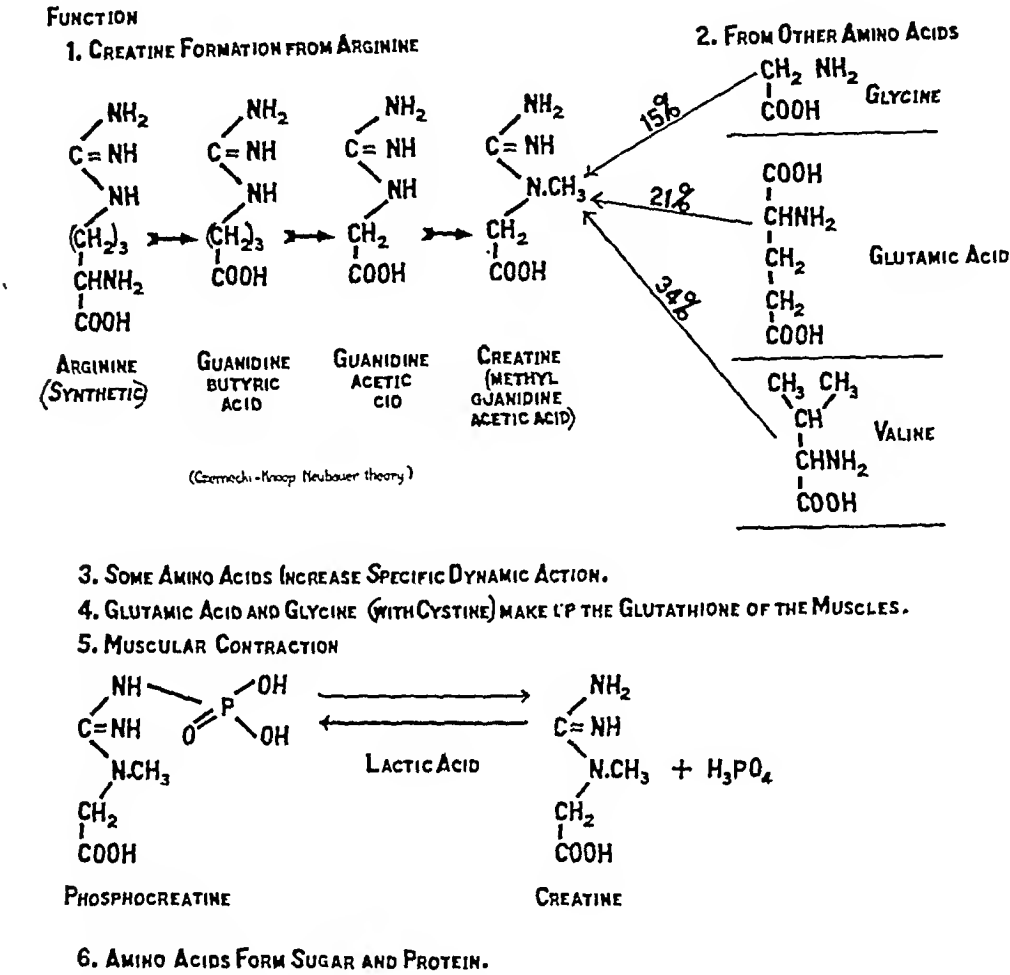


Fig. 7.—Graphic formulas showing the function of arginine and guanidine acetic acid and their conversion into creatine by methylation. The degree of methylation by various amino-acids is indicated by arrows in percentage values. Muscular contraction with its chemistry is graphically represented.

in large doses. These results are in accord with those of other investigators. In our previous study of young rats⁵ in Cleveland it was observed that valine caused an increase of 34 per cent in muscular creatine, cystine, 37 per cent, glycine, 15 per cent, and alanine, 13 per cent. Guanidine acetic acid caused an increase of 48 per cent. Since arginine can be formed synthetically in the body, this may be a source of the guanidine grouping necessary for the formation of the

creatine.²³ We believe that the primary requisite for the formation of the creatine in the body is the methylation of this guanidine rest (possibly as guanidine acetic acid) to creatine. Since valine, with two methyl groups, and cystine, with two substituted methyl groups, produces more than twice as much creatine as glycine (the latter having only one substituted methyl group), it would seem that the degree of methylation per unit of time determines the degree of the formation of the creatine.

This may also explain the formation of creatine from choline and betaine, each of which contains three or more methyl groups. These substances, however, do not produce three times as much creatine as glycine, which may be owing to the fact that there is an upper limit to formation of the creatine from its precursors, in young rats, per unit of time. It is also well known that the body has the power to methylate certain compounds, and it is generally agreed that guanidine acetic acid, even though it does not occur normally in the body, nevertheless can be methylated to creatine when ingested. When this methylation process is increased by the ingestion of amino-acid increased formation of creatine and creatinine results. Therefore, creatine may be formed from ingested amino-acids, or its formation may be stimulated by these amino-acids. In view of the results obtained in our previous work and also in the treatment of patients described in this paper, we believe that creatine arises in the body from both exogenous and endogenous sources.

The formation of creatine is not the only function of the amino-acids. It is well known that glycine and glutamic acid increase the specific dynamic action of protein in the body. These two acids, with cystine, make up the glutathione of the muscles. Finally, each of these amino-acids is capable of forming sugar, and probably both assist in the construction of new proteins in the muscles. These facts are shown by the simultaneous increase in body weight, strength and muscular efficiency in our patients.

A few remarks might be made here on the therapeutic effect of the ingestion of amino-acid on the metabolism of the diseased muscles. The results of our own work and that of many other investigators show that the patient who is suffering from certain types of myopathies cannot

23. This view is in harmony with the well known Czernecki-Knoop-Neubauer theory of the origin of creatine from arginine (Czernecki, W.: *Zur Kenntnis des Kreatins und Kreatinins im Organismus*, *Ztschr. f. phys. Chem.* **44**:294, 1905. Knoop, F.: *Ueber den physiologischen Abbau der Säuren und die Synthese einer Aminosäure im Tierkörper*, *ibid.* **67**:489, 1910. Neubauer, O.: *Abbau der Aminosäuren im Organismus*, in *Abderhalden: Biochemisches Handlexikon*, Berlin, Julius Springer, 1911, vol. 4, p. 360. Hunter, A.: *Creatine and Creatinine*, London, Longmans, Green & Co., 1928, p. 223).

"fix" or retain creatine in the muscles. This valuable substance is continually lost in the urine and is accompanied by a gradual loss of muscle tissue and function. If creatine be given as such, most of it passes through the body and is excreted in the urine. Hence, feeding creatine does not increase the creatine content of the muscles, and no clinical improvement in the patient's condition takes place.

On the other hand, the amino-acids form creatine which at first is lost in fairly large amounts. After a few weeks it is retained in the muscles, and at this time the patient begins to show clinical improvement. It would seem, therefore, that the amino-acids supply a deficiency in muscle metabolism. This creatine, retained as phosphocreatine, serves over and over again to supply the energy for muscle contraction, and the muscular efficiency of the patient increases at a remarkable rate. That the amino-acids play a definite part in muscle metabolism is supported by the fact that as long as they are fed to the patient, he improves, yet this improvement may cease as soon as the therapy is discontinued, and the patient may revert to his original condition. Possibly amino-acids should be given to these patients for the remainder of their lives. However, more experimental evidence is necessary to confirm this opinion.

It is well known that glycine and glutamic acid can be synthesized in the body, and that they are not necessary for growth in the young animal. Nevertheless, it would seem that they play an important part in the metabolism of patients suffering from various forms of muscular dystrophy. More surprising still is the fact that the ingestion of either glycine or glutamic acid is effective. From the results of our previous work, we believe that any amino-acid of the protein molecule may produce similar results. When it is recalled that a protein molecule may contain about twenty amino-acids, it will be seen that nature has provided enough raw material for both muscle structure and function. No doubt it is possible that in the patient with muscular dystrophy (*a*) not enough protein is ingested, (*b*) that which is taken is not utilized to any great extent, (*c*) it is not ingested in the proper form for utilization in muscle metabolism or (*d*) there may be some dysfunction of protein digestion which results in the patient's inability to utilize properly the ingested or formed amino-acids. The latter point is under investigation at the present time, and our results will be published later.

Brentano²⁴ presented evidence to show that creatinuria is always associated with a reduction of the glycogen in the muscle. The disappearance of creatinuria is associated with an increase of glycogen in the muscle. Our clinical results also confirmed the belief that a dis-

24. Brentano, C.: Untersuchungen über die Entstehung der Kreatinurie: II. Mitteilung: Die Beziehungen zwischen Kreatinurie und Muskelglykogen, Arch. f. exper. Path. u. Pharmacol. **155**:21, 1930.

appearance of creatinuria was followed by increase not only of glycogen in the muscles but also of protein. This was shown by the increase in body weight of our patients, after amino-acid therapy. This result has never occurred before while the patients were on their usual full dietary regimen.

It is also possible that the feeding of sugar may stimulate creatine metabolism, since it is generally believed that lactic acid furnishes the energy for the resynthesis of phosphocreatine from creatine and phosphoric acid. Moren⁷ stated that research has shown that in cases of muscular dystrophy a disturbance of sugar metabolism takes place, caused possibly by a lowering of the amount of glycogen in the muscles. Eaton²⁵ and also Farnell²⁵ have noticed beneficial results from feeding sugar to patients suffering from muscular dystrophies.

TABLE 2.—*Classification of Syndromes of Muscular Atrophy and Dystrophy*

Group I. Primary Myopathies:	Group II. Progressive Nuclear Muscular Atrophy:
1. Primary muscular dystrophy (usually of the lower limbs):	1. Mainly of small muscles of the hand (Aran-Duchenne)
(a) Pseudohypertrophic (Duchenne)	2. Hereditary, familial, of infancy and childhood (Werdnig-Hoffmann)
(b) Facio-scapulo-humeral (Landouzy-Dejerine)	3. Subacute and chronic poliomyelitis
(c) Bulbar (Hoffmann)	4. Bulbofacial of childhood (Fazio-Londe)
(d) Juvenile scapular (Erb-Zimmerlin)	5. Progressive bulbar palsy (glosso-labio-laryngeal, of Boucharde)
(e) Infantile-hereditary (Leyden)	6. Chronic progressive ophthalmoplegia (von Graefe)
2. Myasthenia gravis	7. Amyotrophic lateral sclerosis (Dejerine)
3. Amyotonia congenita (Oppenheim)	8. Progressive spinal muscular atrophy
4. Myotonia congenita (Thomsen)	
(a) Early life (hereditary)	
(b) Myotonia acquisita	
5. Myotonia atrophica	

Greater clinical improvement results from amino-acid therapy in the conditions listed in group I than in those listed in group II.

Not only is the classification of the syndromes of muscular atrophy and dystrophy confusing, but not infrequently the names are used interchangeably. Certainly a pathologic-clinical classification is conducive to a much clearer comprehension of the disease processes than is an eponymic classification.

Therefore, we believe that the following classification based on Wechsler's text²⁶ is a satisfactory one (table 2).

It would seem that those conditions listed in group I would be more properly generally classified as dystrophies, and those in group II as atrophies. In other words, the atrophies result from nuclear lesions in the central nervous system, whereas the dystrophies are caused by primary lesions in the muscle which probably are primarily abiotrophic. A review of the cases presented reveals interesting results. Certainly in those cases which fall into the group termed dystrophies, with the excep-

25. Cited by Moren.⁷

26. Wechsler, I. S.: A Text-Book of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1931, p. 191.

tion of the cases of Brand and Harris ¹⁹ in which we believe a meat-free diet low in purine played a most important part in the unsuccessful results, clinical improvement has been uniform. Not only was the progress of the disease in all cases inhibited, but the clinical condition was improved, the improvement being graded as slight, good or marked. The most striking recovery was noted in the cases of myasthenia gravis, pseudohypertrophic muscular dystrophy and progressive muscular dystrophy. On the other hand, the cases which fall into group II seem to be little affected by the administration of the amino-acids. In these cases, the lesions occur primarily in the central nervous system and the atrophy is secondary to the changes in the spinal cord or to nuclear changes. In one of our cases a definite increase in creatinuria occurred with, however, only slight clinical improvement.

The variation in the clinical results in the two groups of cases is most impressive, and it is not unlikely that the clinical results following the administration of amino-acids in sufficient amounts will possibly be additional criteria in distinguishing some of the more vague syndromes so frequently seen, which often defy classification even by the most able neurologists.

In passing, we wish to make a note concerning the use of amino-acids in the diet in cases of poliomyelitis in the acute, convalescent and chronic stages, and also in postpoliomyelitic paralyses. By this therapy we may at least preserve the tone of the paralyzed muscles until regeneration of the affected nerves occurs, and thus prevent the grave atrophic changes that usually result from the lesions of the nerve. Our observations so far have been very encouraging in two cases, but our progress is somewhat slow owing to the small number of cases under observation at the present time. The results, whether positive or negative, will certainly be of interest and will be reported later.

SUMMARY

A review of the recent literature concerning the origin and function of creatine in the muscles, with particular reference to clinical results in patients suffering from various forms of muscular dystrophy and atrophy, is presented.

The clinical results obtained from the administration of glycine or glutamic acid, fed in 10 or 20 Gm. daily doses, in six of our own cases of various dystrophies and atrophies are recorded. The average increases in the excretion of creatine ranged from 48 to 303 per cent, and in the excretion of creatinine from 11 to 46 per cent.

The total number of cases reported by ourselves and others to date is 69, in 51 of which decided clinical improvement has been observed after amino-acid therapy. The most marked clinical improvement is

noted in those cases grouped as muscular dystrophies. Only slight clinical improvement, if any, was noted in cases grouped as progressive nuclear muscular atrophy.

Four possible etiologic factors which may play a part in the pathologic metabolism of the patient with muscular dystrophy are suggested.

It would appear that the administration of creatine is not an effective therapeutic measure.

A new theory of the origin of creatine in the body, based on this and previous work, is presented.

Drs. L. L. Cazenavette, M. S. Freiman, U. Giles, L. S. Hill and H. R. Unsworth permitted the use of their patients; Dr. William M. McCord assisted in the preparation of the amino-acids, and Dean Arthur Vidrine of the medical center gave financial aid which made these studies possible.

BACTERIOLOGIC STUDY OF THROATS IN RHEUMATIC AND NONRHEUMATIC FEVER

WITH SPECIAL REFERENCE TO HEMOLYTIC STREPTOCOCCI

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Clinicians have long recognized that an attack of acute rheumatic fever is preceded in many instances by sore throat or some other infection of the upper respiratory tract. This is true for both an initial attack of the disease and an exacerbation of symptoms. Williams,¹ in discussing this subject, concluded that "the majority of all cases of rheumatic fever are preceded by sore throat or some upper respiratory infection." Observers of this relationship have further noted that the rheumatic symptoms do not immediately follow the respiratory infection, but that there is an interval of from ten to twenty-one days. Recently a number of careful investigators called attention to the presence of hemolytic streptococci in the throats of persons who later manifest the symptoms of acute rheumatic fever. They laid great emphasis on this point, believing that an etiologic relationship exists. An equally careful group of observers, however, believe that such a conclusion at the present time is unwarranted. Some maintain that green-producing streptococci are the causative agents; others think that no single streptococcus, but rather an entire group, is responsible for the symptoms of the disease, and still others insist that an agent unrelated to the streptococci, as, for example, a filtrable virus, plays the important rôle.

The present study was undertaken with a view to gathering further data on the presence of hemolytic streptococci in the throats of patients with rheumatic fever and to attempt to correlate, if possible, their presence with the clinical symptoms of the disease. A large number of controls were included in the study. There were certain inherent

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This work was done under the tenure of the Lionel and Florentine Scholle Sutro Fellowship.

From the Medical Division of Montefiore Hospital for Chronic Diseases, and the Department of Bacteriology, New York University and Bellevue Hospital Medical College.

1. Williams, A. W.: *Streptococci in Relation to Man in Health and Disease*, Baltimore, Williams & Wilkins Company, 1932.

difficulties in the problem which soon became apparent. One of them was pointed out by Andrews, Derick and Swift² in 1926. They called attention to the fact that a large number of patients with rheumatic fever who enter a hospital do so after they have completely recovered from infection of the throat. Of 122 patients with rheumatic fever who were admitted to the hospital of the Rockefeller Institute, only 5 had active infection of the throat at the time of admission. A second difficulty lies in the fact that the symptoms of the upper respiratory tract may be so mild as to be overlooked, and therefore no history of any such symptoms is obtained when the patient is admitted to the hospital. This is especially true in the case of young children. In addition, a bacteriologic examination of throats after the acute infection has subsided does not always reveal the causative organism. The flora of the throat, especially as regards pathogenic organisms, is by no means constant. Coburn and Pauli,³ in their study of the throats of patients with rheumatic fever, observed that *Streptococcus haemolyticus* tended to become conspicuous during the quiescent phase of the disease and absent during an exacerbation of symptoms. In spite of these difficulties, a number of investigators have insisted that the time when an exacerbation of rheumatic symptoms would appear might be predicted with a fair degree of accuracy by ascertaining the presence of hemolytic streptococci in the throat.

REVIEW OF THE LITERATURE

In 1886, Haig-Brown,⁴ the medical officer at a boys' school in England, observed that "an attack of acute rheumatism is very frequently preceded by one of acute tonsillitis." The interval might be five or six weeks, but usually it was ten days or a fortnight. The two diseases might even be coincident. He also noted that among 345 previously healthy boys with tonsillitis, heart disease developed in 21.

There is a wide difference of opinion among observers as to the effect of tonsillectomy in preventing attacks of acute rheumatic fever. In 1920, St. Lawrence⁵ stated that "tonsillectomy would seem to be the most important measure at present available for the prevention of

2. Andrews, C. H.; Derick, C. L., and Swift, H. F.: A Study of Hemolytic Streptococci in Acute Rheumatic Fever, *J. Exper. Med.* **43**:13, 1926.

3. Coburn, A. F., and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process; Observations on Ecology of Hemolytic Streptococcus in Relation to Epidemiology of Rheumatic Fever, *J. Exper. Med.* **56**:609, 1932.

4. Haig-Brown, C.: Tonsillitis in Adolescents, London, Baillière, Tindall & Cox, 1886.

5. St. Lawrence, W.: Effect of Tonsillectomy on the Recurrence of Acute Rheumatic Fever and Chorea, *J. A. M. A.* **75**:1035 (Oct. 16) 1920.

acute rheumatic fever." Eighty children were observed during an average period of three and a half years following tonsillectomy. One or more attacks of acute rheumatic fever had occurred in 42 before the tonsils were removed. After tonsillectomy there was no recurrence in 35, or 84 per cent.

In the same year, Poynton, Paterson and Spence,⁶ in England, found that removing the tonsils did not prevent the recurrence of the disease. They pointed out, however, that the throat is a common portal of entry for the rheumatic infection. They based this conclusion on a study of 172 rheumatic children. In 22 of the cases acute tonsillitis had immediately preceded the attack of rheumatism; in 38 there were large and unhealthy tonsils, and in 17 the tonsils had been removed.

Ingerman and Wilson⁷ also studied the relationship between tonsillectomy and the occurrence of rheumatic manifestations. They found that 76 per cent of 88 cases of tonsillitis were followed by a recurrence of rheumatic manifestations within from one to eleven years after tonsillectomy. In a group of 97 patients on whom tonsillectomy had not been performed and who were studied over a similar period, 80 per cent showed a recurrence of rheumatic manifestations.

Kaiser⁸ followed for a period of three years a group of 1,200 children who had had their tonsils removed and an equal number who had had no operation. He concluded that tonsillectomy had not influenced the incidence of chorea or rheumatism. A history of rheumatic symptoms had been obtained from 46 children previous to the operation. Three years later, 129 had similar disorders, and of this number 116 had their first attack of rheumatism after the operation. In the group not operated on, 128 had rheumatic symptoms.

Mackie⁹ noticed that complete removal of the tonsils when evidence of infection was present, together with appropriate treatment of other foci of infection, seemed to reduce but did not wipe out recurrences of rheumatic fever. Of 80 patients whose tonsils had been enucleated after an attack of acute rheumatic fever, 34, or 42.5 per cent, had recurrences. This group had been observed for about three years. Of 207 patients on whom tonsillectomy had not been performed, 125, or 60.3 per cent, had recurrences. This group had been observed over four years.

6. Poynton, F. J.; Paterson, D., and Spence, J. C.: Acute Rheumatism in Children, *Lancet* **2**:1086, 1920.

7. Ingerman, E., and Wilson, M. G.: Rheumatism: Its Manifestations in Childhood Today, *J. A. M. A.* **82**:759 (March 8) 1924.

8. Kaiser, A. D.: Effect of Tonsillectomy on the General Health of 1,200 Children, as Compared with an Equal Number Not Operated On, *J. A. M. A.* **83**:33 (July 5) 1924.

9. Mackie, T. T.: Rheumatic Fever: An Analytical Study of 393 Cases of Rheumatic Fever and 89 Cases of Chorea, *Am. J. M. Sc.* **172**:199, 1926.

Boas and Schwartz,¹⁰ in 1927, studied the records of 53 children under 15 years of age with rheumatic heart disease at Montefiore Hospital. Thirty-nine of these patients had febrile episodes. The authors found that 20 of these 39 patients and 10 of the remaining 14, who had been afebrile, had had their tonsils removed. In addition, only 10 of the 63 episodes of fever exhibited by the 39 patients were associated with tonsillitis. They concluded that the tonsil is not so important a portal of entry for rheumatic infection as has been generally supposed and that tonsillectomy appears to be of little avail in reducing the hazards of reinfection.

Irvine-Jones¹¹ made cultures from the throats of rheumatic children and found that hemolytic streptococci were usually present during convalescence and only rarely during the period of acute sore throat. The streptococci obtained from the upper respiratory tract of rheumatic children were identical with those from normal children.

McCulloch and Irvine-Jones¹² studied 150 children at the Children's Heart Clinic of Washington University over periods varying from nine months to eleven years. In this group attacks of rheumatic fever or chorea occurred 304 times. One hundred and ninety-seven of these attacks had apparently been precipitated by colds or sore throats. The authors believed that tonsillectomy, when followed by hygienic measures, is of value in decreasing the number of recurrences of rheumatic fever and chorea. In a group of 90 children with constant infection in the nasopharynx, the percentage of recurrences of rheumatic fever and chorea was paralleled by the success obtained in combating the infection and improving the living conditions of the patients.

Nabarro and MacDonald,¹³ in 1929, made repeated cultures from the tonsils of 50 rheumatic and 48 nonrheumatic children. They found that the streptococci isolated from the tonsils of the subjects with rheumatism did not differ materially from those isolated from the tonsils of the subjects free from rheumatism. Even when the cultures were grown on Crowe's medium,¹⁴ which is supposed to bring out the most minute differences in the appearance of the colony, these investigators

10. Boas, E. P., and Schwartz, S. P.: Some Modes of Infection in Rheumatic Fever, *Am. Heart J.* **2**:375, 1927.

11. Irvine-Jones, E. I. M.: Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates and Its Relationship to Rheumatic Fever, *Arch. Int. Med.* **42**:784 (Nov.) 1928.

12. McCulloch, H., and Irvine-Jones, E. I. M.: The Rôle of Infection in Rheumatic Children, *Am. J. Dis. Child.* **37**:252 (Feb.) 1929.

13. Nabarro, D., and MacDonald, R. A.: Bacteriology of the Tonsils in Relation to Rheumatism in Children, *Brit. M. J.* **2**:758, 1929.

14. Crowe, H. W.: Differentiation and Classification of Non-Haemolytic Streptococci by Use of Crowe's Medium, *Ann. Pickett-Thomson Research Lab.* **3**:251, 1927.

were unable to differentiate the organisms obtained from the two sources. They therefore concluded that no specific streptococcus is the cause of rheumatism.

Glover¹⁵ called attention to an epidemic of tonsillitis in the Royal Air Force at Halton, England, in 1928. Four hundred and twenty-seven patients were admitted to the hospital. There were 41 cases of acute rheumatism, in 17 of which there were symptoms of carditis. It was observed that the peak of the tonsillitis epidemic preceded by some two or three weeks the crest of the epidemic of acute rheumatism.

Schlesinger,¹⁶ as a result of a four year clinical study of the relationship between infection of the throat and rheumatic relapses at the West Wickham Hospital for children with rheumatic heart disease, concluded that relapses are largely brought about by acute and often extremely mild infections of the throat. In a group of 62 rheumatic patients with tonsillitis, 40 showed no sequelae. The remaining 22, however, after an approximate interval of from ten to twenty-one days, showed a rise in temperature and a relapse of rheumatism. For several months previous to the attack of tonsillitis these patients had had quiescent valvular lesions and a normal temperature and pulse rate. The streptococci recovered from the tonsils were occasionally hemolytic, but for the most part they were of the viridans type that is commonly found in normal throats. Schlesinger therefore did not favor the theory that a specific streptococcus is the cause of rheumatism but was more inclined to the view that the whole group of these micro-organisms is in some way responsible. He observed that children who had had their tonsils removed were less prone to nasopharyngeal infections than those who retained them. However, tonsillectomy did not preclude acute infection of the throat, and when this did occur there seemed to be greater likelihood of a rheumatic relapse. Recurrences following acute nasopharyngeal infection were observed in 50 per cent of the children who had had the operation and in only 30 per cent of those who had not. The severity of the relapses in both groups was about the same.

Sheldon¹⁷ reported a two year clinical study of children with rheumatism at the Cheyne Hospital for Children and the Lancing Convalescent Heart Home. He confirmed Schlesinger's observation that if a child has had a rheumatic infection a relapse is likely to follow an acute infection of the throat within, roughly, from ten to twenty-one days. He also found that removal of the tonsils did not influence the

15. Glover, J. A.: Milroy Lectures on Incidence of Rheumatic Diseases: Incidence of Acute Rheumatism, *Lancet* **1**:499, 1930.

16. Schlesinger, B.: The Relationship of Throat Infection to Acute Rheumatism in Childhood, *Arch. Dis. Childhood* **5**:411, 1930.

17. Sheldon, W.: On Acute Rheumatism Following Tonsillitis, *Lancet* **1**:1337 (June 20) 1931.

likelihood of a rheumatic relapse. He was not able to confirm the finding of Schlesinger that the continued administration of acetylsalicylic acid following tonsillitis would prevent any serious rheumatic relapse.

Collis¹⁸ investigated the flora of the throat in the epidemic of tonsillitis that was described by Sheldon at the Cheyne Hospital for Children. He found that rheumatic relapses occurred in 9 of 11 children in whom hemolytic streptococcic sore throat had developed. In those who had an infection of the upper respiratory tract associated with some organism other than the hemolytic streptococcus there were no relapses.

Glover and Griffith¹⁹ described two epidemics of acute rheumatism in the English public schools. In the first there were 136 cases of sore throat, 15 of which were followed by acute rheumatism (the proportion being slightly greater than 1 in 10). Tonsillar and pharyngeal cultures from 8 of these patients with rheumatism were examined. Five of them yielded hemolytic streptococci, all of the same serologic type. A year later there was another outbreak of tonsillitis. Hemolytic streptococci were found in 77 cases, the majority of which were of one serologic type, but this type was different from that found the previous year. In 6 of these cases rheumatic symptoms appeared.

Swift²⁰ observed that most patients, both children and adults, give a history of repeated nonspecific infections of the respiratory tract, including the tonsils, sinuses and middle ear, extending over several years, before a typical attack of rheumatic fever is ushered in by a severe focal infection.

Coburn²¹ and Coburn and Pauli³ reported the results of an extensive series of observations on the incidence of acute rheumatic fever. They believed that there is a close relationship between the presence of hemolytic streptococci in the throats of patients with this disease and the occurrence of rheumatic symptoms. They found that in tropical environments hemolytic streptococci are unusual in the flora of the throat and that rheumatic fever is rare. On the other hand, in New York City, where these organisms are frequently found, there are numerous cases of the disease. When the streptococcus becomes implanted in the throat there may be either no symptoms or, possibly, only those of a slight cold. In the majority of persons this local disease is the only manifestation of the invasion of the tissues. In a small

18. Collis, W. R. F.: Acute Rheumatism and Haemolytic Streptococci, *Lancet* **1**:1341 (June 20) 1931.

19. Glover, J. A., and Griffith, F.: Acute Tonsillitis and Some of Its Sequels, *Brit. M. J.* **2**:521, 1931.

20. Swift, H. F.: Factors Favoring the Onset and Continuation of Rheumatic Fever, *Bull. New York Acad. Med.* **7**:429, 1931.

21. Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Baltimore, Williams & Wilkins Company, 1931.

minority, however, this is followed by acute rheumatic fever. These investigators concluded from a study of ambulatory rheumatic patients over a period of four years that persons who escape respiratory disease remain free from rheumatic symptoms and that the majority of patients who contract hemolytic streptococcic pharyngitis have shortly afterward a definite recrudescence of rheumatism.

Bradley²² reported two epidemics of acute rheumatism in an English school which had been free from such infection for about forty years. The epidemics were paralleled by waves of hemolytic streptococcic sore throat. Prior to these epidemics *Streptococcus haemolyticus* had rarely been detected.

Paul and Salinger²³ carefully studied the histories of 15 families in which the incidence of rheumatic fever was high. From their own evidence and from that obtained from other investigators they concluded that rheumatic fever is an infectious disease. Environmental factors probably play an important part, because flare-ups seem to sweep through a family in recurrent waves. These investigators thought that droplet infection attendant on disease of the upper respiratory tract may be responsible for the spread of the unknown virus. During the epidemic waves children between the ages of 4 and 12 seem to be particularly susceptible to the disease. The last point was elaborated in a subsequent paper by Paul.²⁴

PROCEDURE

The cases studied were from Montefiore Hospital and Bellevue Hospital,²⁵ New York City. At Montefiore Hospital the patients were distributed in five wards and in the convalescent pavilion. Those in the pavilion were ambulatory, whereas those in the wards were for the most part confined to bed. Each ward has eighteen beds, and there are a number of smaller rooms adjoining, each containing from two to seven beds. Visitors are permitted twice a week for two hours. The possibility of contact infection exists. No cultures were made from the throats of visitors to the wards, however. In Bellevue Hospital, two children's wards were studied. Each ward is divided into nineteen cubicles and contains approximately thirty-two beds. Visiting hours are two hours twice a week.

The throat cultures included tonsillar, pharyngeal and nasopharyngeal swabs. For a time cultures were taken from two different sources.

22. Bradley, W. H.: Epidemic Acute Rheumatism in a Public School, *Quart. J. Med.* **1**:79, 1932.

23. Paul, John R., and Salinger, R.: The Spread of Rheumatic Fever Through Families, *J. Clin. Investigation* **10**:33, 1931.

24. Paul, John R.: Age Susceptibility to Familial Infection in Rheumatic Fever, *J. Clin. Investigation* **10**:53, 1931.

25. Dr. Charles Hendee Smith, Director of the Pediatrics Division of Bellevue Hospital, permitted us to study the cases in his service.

It was found that the nasopharyngeal swabs yielded slightly better results than the others, and this method alone was used in the later cultures. The swabs were placed in dry sterile tubes and were brought to the laboratory. At first duplicate swabs were placed in tubes of various culture mediums during their transportation, but it was found that the results were practically the same as when a dry tube was used, and this method was discontinued.

Davis,²⁶ in 1912, studied tonsillar cultures in a series of persons suffering from chronic articular, renal and cardiac diseases and from chronic tonsillitis. He observed that surface cultures only occasionally showed hemolytic streptococci, whereas cultures made from the crypts of extirpated tonsils revealed this organism much more frequently. Pilot and Davis,²⁷ in 1919, apparently confirmed this observation; they reported hemolytic streptococci in 61 per cent of swab cultures and in 97 per cent of cultures taken from the crypts of excised tonsils. These tonsils were not normal. The same authors called attention to the fact that in swab cultures of normal tonsils Ruediger²⁸ found hemolytic streptococci in 59 per cent and Smillie²⁹ in 50 per cent, and that in cultures made directly from the crypts Nichols and Bryan³⁰ found them in 50 per cent. They were rather loath to accept this similarity of results and attempted to explain it on the ground that it is difficult to make cultures directly from the crypts with the tonsils in situ. In 1921, Pilot and Pearlman³¹ emphasized this point by reporting hemolytic streptococci in 55 per cent of nasopharyngeal swabs and swabs from the surfaces of the adenoids, whereas cultures from the excised tonsils of the same patients yielded positive results in 95 per cent.

In our study it was not possible to make cultures from the excised tonsils. When tonsillar swabs were made, the tonsil was compressed in order to force to the surface any material that might be in the crypts. We appreciate that this is not so effective as making cultures directly from the crypts in the excised tonsils. However, it seems to be of some importance to note the percentage of persons in whom hemolytic strep-

26. Davis, D. J.: *Bacteriology and Pathology of the Tonsils*, J. Infect. Dis. **10**:148, 1912.

27. Pilot, I., and Davis, D. J.: *Hemolytic Streptococci in the Faucial Tonsil and Their Significance as Secondary Invaders*, J. Infect. Dis. **24**:386, 1919.

28. Ruediger, G. F.: *Streptococci from Scarlatinal and Normal Throats and from Other Sources*, J. Infect. Dis. **3**:755, 1906.

29. Smillie, W. G.: *Studies of the Beta Hemolytic Streptococcus*, J. Infect. Dis. **20**:45, 1917.

30. Nichols, H. J., and Bryan, J. H.: *The Tonsils as Foci of Infection in Streptococcus Hemolyticus Carriers*, J. A. M. A. **71**:1813 (Nov. 30) 1918.

31. Pilot, I., and Pearlman, S. J.: *Bacteriologic Studies of the Upper Respiratory Passages*, J. Infect. Dis. **29**:47, 1921.

tococci invade the surface of the tonsils and the nasopharynx, in contradistinction to those who show them only in the deep recesses of the tonsils, which, according to the authors just quoted, seems to be the universal finding.

A streak plate and two or three dilution pour plates were made of each culture. The plates were prepared in the following manner: A swab was placed in a small amount of veal infusion broth with a p_H of from 7.6 to 7.8 and was rotated to remove organisms. The swab was then removed from the broth and was rolled over a blood veal infusion agar plate, from which a streak was subsequently made. From the veal infusion broth two or three standard blood agar pour plates were made. The original veal broth was so diluted that at least one pour plate would be likely to have a good seeding. The pour plates were made of 12 cc. of veal infusion agar with a p_H of from 7.6 to 7.8, cooled to from 40 to 42 C., and 5 per cent of horse blood plus the dilution of the organism. The pour plates were incubated aerobically for forty-eight hours; the streak plates, for from twenty-four to forty-eight hours.

In 107 cultures, or 13 per cent, duplicate agar pour plates were made with rabbit blood and horse blood to ascertain whether there was an advantage in the rabbit blood. Forty-eight cultures, or slightly less than half the total number, showed hemolytic streptococci. In 12 cultures the rabbit blood appeared to favor the development of *Streptococcus haemolyticus* more than the horse blood; in 7 cultures the reverse held true, while in 21 cultures the blood from the two specimens appeared to be of approximately equal value for the development of these organisms. Variations were observed in the degree of hemolysis produced in the two kinds of blood by the same cultures. Six cultures showed hemolytic streptococci in the rabbit blood agar pour plates and not in the horse blood agar pour plates, while 2 cultures showed colonies of hemolytic streptococci in the horse blood agar but not in the rabbit blood agar. Furthermore, in some cases the rabbit blood seemed better suited for the development of throat flora. In general, it would appear that rabbit blood is slightly better than horse blood; but if appropriate dilutions are made of the culture in the preparation of pour plates, the species of animal from which the blood is obtained seems to be of relatively slight importance. In arriving at this conclusion we realized that our method was one which would give at best only a rough quantitative index of hemolytic streptococci. Moreover, none of our glassware was calibrated, and slight errors in volumetric measurements would color our results. However, our aim was to develop not an exact quantitative procedure but a reliable qualitative method which would also serve as a quantitative estimate. The medium recommended by Mueller and

Whitman³² was also tried but was not found so satisfactory as the veal infusion base.

All the plates were examined by the aid of a binocular culture microscope, and many of the hemolytic colonies were examined for more detailed characters with the low power of a compound microscope. The streak plate was used for rough differentiation and for the detection of various groups of organisms. The pour plate was used for the detection of *Streptococcus haemolyticus*. The colonies were classified as hemolytic, green-producing and indifferent. The percentage of incidence of each class, as well as the total growth per plate, was recorded. Of the colonies producing hemolysis, 3 or more specimens of each type were examined microscopically and were subcultured on blood agar plates. This procedure was followed to ascertain whether hemolytic organisms other than *Streptococcus haemolyticus*, such as *Hemophilus haemolyticus*³³ were present. To check the question of hemolysis a pour plate of one of the pure subgenerations of each type of organism was made. In addition, hemolysin tests were carried out with tubes. Hemolysis, as evidenced in the pour plates and in the tubes, checked in all but 3 cultures. These cultures have not been included in our tabulations of hemolytic streptococci.

In the latter part of our work, in addition to the regular examination of the streak and pour plates, more detailed observations of colonies and more detailed morphologic observations were made in order to determine the percentage of incidence of *Hemophilus haemolyticus*, diphtheroids, pneumococci and staphylococci. Ten per cent of 163 cultures yielded hemolytic organisms of the type *Hemophilus haemolyticus*. Eleven patients showed these organisms; all were suffering from rheumatic fever. In pour plates as well as in streak plates the colonies of *Hemophilus haemolyticus* could be differentiated from those of hemolytic streptococci. Whereas the deep colony of the hemolytic streptococcus in transmitted light was either biconvex, triangular or rosette-like and was large, dark, grayish white, dense, opaque and granular throughout, the deep colony of *Hemophilus haemolyticus* was always simple and was smaller, much lighter in appearance, almost translucent and relatively smooth, the surface only appearing somewhat granular. Diphtheroids were present in 22 per cent of 172 cultures. Eleven per cent of 131 cultures showed organisms which resembled morphologically and colonially the pneumococcus and which were soluble in bile. In 4 per cent of 181 cultures hemolytic staphylococci predominated.

32. Mueller, J. H., and Whitman, L.: An Improved Method for the Detection of Hemolytic *Streptococcus* Carriers, *J. Bact.* **21**:219, 1931.

33. Pritchett, I. W., and Stillman, E. G.: Occurrence of *Bacillus Influenzae* in Throats and Saliva, *J. Exper. Med.* **29**:259, 1919.

RESULTS

The number of cases from Montefiore Hospital recorded in this report is 261. The total number of cultures is 727. The investigation covered parts of three years—1931, 1932 and 1933—but the greater number of cases was studied during the winter and spring of 1932. Owing to the mildness of the winter of 1931-1932 (which was the warmest in more than one hundred years, east of the Rocky Mountains, according to the United States Weather Bureau charts) and to the relatively few cases of infection of the upper respiratory tract which developed in the hospital, the investigation was continued during the winter and spring of 1932-1933. However, during this period no great number of infections of the upper respiratory tract appeared among the hospital population. During the period 1931-1932 one slight epidemic of infection of the upper respiratory tract occurred. It started on February 26, 1932, continued with little, if any, abatement through March 3 and had completely subsided by March 28. At Bellevue Hospital the number of cases and the number of cultures were 60 and 113, respectively. The period of investigation was from February 1 to May 11, 1932. No epidemics were reported in the two wards in which these patients were located. The months during which cultures were obtained from Montefiore Hospital were December, 1931, the first six months of 1932 (through June 1) and the first four months of 1933. The greatest number of cultures for any single month was taken in March, 1932. Thus the seasonal incidence of the cultures coincided with the season of the year when increases in acute attacks of rheumatic fever were found most likely to occur.

The cases from Montefiore Hospital have been grouped in five broad diagnostic divisions. Group 1 includes ward patients suffering from active or chronic rheumatic fever and is designated as the chronic rheumatic cardiovalvular disease (CRCVD) group. It includes 101 cases and 390 cultures. These cases represent 39 per cent of all cases, and the cultures represent 54 per cent of the total number of cultures. The age of the members of the group varies from 3 to over 60 years of age. Fifty-three per cent of the patients were males, and 47 per cent were females. Tonsillectomy had been performed on 61 per cent of the group.

The other four groups are control groups and include ward patients suffering from conditions unrelated to rheumatic fever (groups 2, 3 and 4) and normal persons (group 5), composed of doctors, nurses and attendants on duty at the hospital. These four groups include 160 cases and 337 cultures and represent 61 and 46 per cent of the total number of cases and cultures, respectively. Group 2 includes persons suffering from arthritis, other than that caused by acute rheumatic fever. The cases in this division represent only 2 per cent of the total number,

and the cultures represent the even smaller number of 1 per cent. Group 3, known as the group of "other cardiac conditions," is composed chiefly of cases of hypertension, arteriosclerosis, disease of the coronary arteries and subacute bacterial endocarditis (4 cases). This group comprises 81 cases (31 per cent) and 183 cultures (25 per cent). The age range is higher here than in the other groups. In Group 4 have been placed all the manifestations of disease not recorded elsewhere. It is known as the division of "other conditions." Analysis of this division shows 59 cases (23 per cent) and 129 cultures (18 per cent). The most frequent diseases are diabetes mellitus, nephritis and cirrhosis of the liver, but there are in all 32 different diseases. These include such conditions as Banti's disease, lesions of the brain, Cooley's anemia, encephalitis, exophthalmic goiter, kala-azar, pulmonary abscess, osteomyelitis, pyelitis, tuberculosis and ulcerative colitis. Group 5 includes 17 cultures taken from 14 normal persons. These constitute 5 per cent of the cases and 2 per cent of the cultures.

In the control groups 66 per cent of the subjects were males, as compared with 53 per cent in the group with chronic rheumatic cardiovalvular disease. Tonsillectomy was known to have been performed in only 27 per cent of the cases, as against 61 per cent in the rheumatic group.

Forty-seven per cent of all the subjects, or 114, had one throat culture. The remaining 46 per cent, or 67 subjects, had from 2 to 20 repeat cultures. Analysis of this 46 per cent on the basis of the individual groups shows that 68 per cent of the patients with rheumatic fever had 2 or more repeat cultures per case. By making frequent cultures from the throats of the patients who were suffering from rheumatic fever it was hoped to obtain more definite information concerning the presence of hemolytic streptococci in infections of the throat and thereby to correlate, if possible, their presence during this period with an exacerbation of the disease. The mean number of cultures per case is 2.8; for group 1 it is 3.9, and for the control groups, 2.1.

The cases and cultures from Bellevue Hospital were analyzed in the same manner. There were no cases of arthritis, but there were a number of patients with chorea. No person in any of the groups was over 14 years of age. In the group of patients with chronic rheumatic cardiovalvular disease there were 34 cases and 82 cultures. There were also 14 cases of chorea, 3 of cardiac conditions not due to rheumatic fever and 9 of other diseases. The number of cultures in each of these groups was 17, 5 and 9, respectively. Two of the 3 subjects suffering from other cardiac conditions had subacute bacterial endocarditis. Other diseases included nephritis, pemphigus, encephalitis, diabetes mellitus, pneumonia and epilepsy. Fifty-six per cent of the patients with chronic rheumatic cardiovalvular disease were males; ton-

sillectomy had been performed on 68 per cent. In the other groups, 35 per cent were males; 46 per cent had had their tonsils removed. The number of repeat cases ranged from 2 to 6, but only 4 of the controls had more than 1 culture. Among the patients with rheumatic fever 28 had repeat cultures. The mean number of cultures per case was 2.1.

For a full and perhaps more exact interpretation of the data, it seemed desirable to analyze the material in terms of subjects and the total number of throat cultures and to divide all groups into three age divisions. The following classifications were made: subjects under 15 years of age, those between 15 and 29 years and those 30 years of age and over. All the patients from Bellevue Hospital were under 15 years of age.

TABLE 1.—*Incidence of Cases and Cultures According to Age (Montefiore Hospital)*

Group	Cases			Cultures		
	14 Years and Below	15-29 Years	30 Years and Above	14 Years and Below	15-29 Years	30 Years and Above
1. Chronic rheumatic cardiovalvular disease..	41 (40%)	21 (21%)	39 (39%)	231 (59%)	79 (20%)	80 (21%)
2. Arthritis.....	0	1 (17%)	5 (83%)	0	2 (25%)	6 (75%)
3. Other cardiac conditions.....	2 (3%)	6 (7%)	73 (90%)	4 (2%)	21 (12%)	153 (86%)
4. Other conditions.....	16 (27%)	7 (12%)	36 (61%)	43 (33%)	17 (13%)	69 (54%)
5. Normal persons.....	0	13 (93%)	1 (7%)	0	16 (94%)	1 (6%)
Total.....	59 (23%)	48 (18%)	154 (59%)	278 (38%)	135 (19%)	314 (43%)

Table 1 shows the incidence of cases and cultures from Montefiore Hospital according to age. Of the 101 subjects suffering from chronic rheumatic cardiovalvular conditions, 41 (40 per cent) had active cases and were under 15 years of age; 21 (21 per cent) were between 15 and 29, and 39 (39 per cent) had chronic cases and were 30 years old or more. Of the 390 cultures, 231 (59 per cent) were taken from members of the first group, 79 (20 per cent) from members of the second group and 80 (21 per cent) from the last group. Thus there were available for study a fair number of cases of rheumatic fever in each age group. Of the total number of cases and cultures from the group of patients with rheumatism, more than one-third and one-half, respectively, fall in the group under 15 years of age. The total number of control subjects under 15 years in the four groups is slightly less than half the number in the group of subjects with rheumatic fever, and the total number of cultures equals, roughly, one-fifth the number of those in group 1. The cases and cultures in the controls between 15 and 29 years are more numerous, but no single division approximates the number in the rheumatic fever group.

In table 2 the data from Montefiore Hospital are analyzed with reference to the occurrence of hemolytic streptococci in the throat cultures and throats of the subjects. No age groups are observed; these have been left to a later analysis in which the question of correlation between infection of the upper respiratory tract and the presence of hemolytic streptococci is considered. From a study of the data, it appears that *Streptococcus haemolyticus* is found no more frequently in the throat cultures of persons suffering from rheumatic fever than in those of other persons. Hemolytic streptococci seem to be present in about 25 per cent of the throat cultures of the hospital population. When an analysis is made in terms of subjects rather than of the total number of cultures and a comparison is made with the former data, it is observed that as repeat cultures are taken from the same group of hospital

TABLE 2.—*Incidence of Hemolytic Streptococci in Throat Cultures and Throats (Montefiore Hospital)*

Group	Cases			Cultures		
	Total	Incidence of Hemolytic Streptococci		Total	Incidence of Hemolytic Streptococci	
		Present	Absent		Present	Absent
Chronic rheumatic cardiovalvular disease.....	101*	43 (43%)	57 (56%)	390*	86 (22%)	303 (77%)
Arthritis.....	6	0	6 (100%)	8	0	8 (100%)
Other cardiac conditions.....	81	31 (38%)	50 (62%)	183	52 (28%)	131 (72%)
Other conditions.....	59*	17 (29%)	41 (70%)	129*	29 (22%)	99 (77%)
Normal persons.....	14	2 (14%)	12 (86%)	17	5 (29%)	12 (71%)
Total controls.....	160	50 (31%)	109 (68%)	337	86 (26%)	250 (74%)
Total.....	261	93 (36%)	166 (64%)	727	172 (24%)	553 (76%)

* One culture showed no growth.

patients there is a tendency for positive results to increase. It appears from table 2 that the tendency is more marked in patients with rheumatic fever than in patients suffering from other diseases. The percentage of persons with rheumatic fever who give throat cultures which are positive for hemolytic streptococci is 43. The highest percentage in any control group is 38, and the total for all the control groups is 31. However, in formulating these conclusions account must be taken of the fact that the number of patients with rheumatic fever and the number of throat cultures from this group are greater than in any control group and that 68 per cent of the patients with rheumatic fever, as against less than 50 per cent of the controls, had repeat cultures. Thus the higher percentage of hemolytic streptococci in the rheumatic fever group may be merely apparent, and the percentages in the various groups might be more nearly equal if large numbers of throat cultures from nonrheumatic subjects had been taken.

The data from Bellevue Hospital (table 3) have been collected in a similar manner. The control groups are small. Because of this they

have been considered not only individually but also collectively. Just as with the material taken from Montefiore Hospital, there is a tendency for throat cultures which are positive for hemolytic streptococci to increase as repeat cultures are taken from the same group of subjects. This trend is more marked in the group from Bellevue Hospital than in that from Montefiore Hospital. These differences may be partly

TABLE 3.—*Incidence of Hemolytic Streptococci in Throat Cultures and Throats (Bellevue Hospital)*

Group	Cases			Cultures		
	Total	Incidence of Hemolytic Streptococci		Total	Incidence of Hemolytic Streptococci	
		Present	Absent		Present	Absent
Chronic rheumatic cardiovalvular disease.....	34	20 (59%)	14 (41%)	82	31 (38%)	51 (62%)
Chorea.....	14	4 (29%)	10 (71%)	17	4 (23%)	13 (77%)
Other cardiac conditions.....	3	0	3 (100%)	5	0	5 (100%)
Other conditions.....	9	6 (67%)	3 (33%)	9	6 (67%)	3 (33%)
Total rheumatic.....	48	24 (50%)	24 (50%)	99	35 (35%)	64 (65%)
Total nonrheumatic.....	12	6 (50%)	6 (50%)	14	6 (43%)	8 (57%)
Grand total.....	60	30 (50%)	30 (50%)	113	41 (36%)	72 (64%)

TABLE 4.—*Percentage of Incidence of Colonies of Hemolytic Streptococci in Throat Cultures (Montefiore Hospital) **

Group	Total Number of Cultures	Total Cultures Showing Hemolytic Streptococci	1-10%	11-20%	21-30%	31-40%	41-50%	Above 50%
Chronic rheumatic cardiovalvular disease.....	390	86	51 (59%)	10 (12%)	7 (8%)	6 (7%)	2 (2%)	10 (12%)
Arthritis.....	8	0						
Other cardiac conditions.....	183	52	29 (56%)	5 (10%)	7 (13%)	7 (13%)	..	4 (8%)
Other conditions.....	129	29	20 (69%)	1 (3%)	2 (7%)	3 (10%)	1 (3%)	2 (7%)
Normal persons.....	17	5	2 (40%)	3 (60%)

* The percentages are based on the number of cultures which showed hemolytic streptococci.

accounted for by the fact that the patients from Bellevue Hospital were either children or adolescents, whereas the subjects with rheumatic fever from Montefiore Hospital included 51 adults.

The next question of interest is whether patients suffering from rheumatic fever have a greater percentage of hemolytic streptococci in their throats than do other persons. In table 4 data are given which relate to this subject. The patients from Bellevue Hospital have been omitted in this analysis, as the number of controls is too small for a basis of comparison. The cultures from each diagnostic group have

been divided into six subdivisions according as the percentages of hemolytic streptococci comprised, roughly, from 1 to 10 per cent, from 11 to 20 per cent, from 21 to 30 per cent, from 31 to 40 per cent, from 41 to 50 per cent or more than 50 per cent of the total throat flora, as ascertained by dilution pour plates. The percentages of each division have been obtained by using the total number of cultures showing hemolytic streptococci in each diagnostic group. The table shows that there is no tendency for hemolytic streptococci to occur more abundantly in the throats of patients with rheumatic fever than in those of other patients. In fact, in this study *Streptococcus haemolyticus* seems to occur slightly more abundantly in the throat cultures of subjects suffer-

TABLE 5.—*Incidence and Preponderance of Green-Producing and Indifferent Streptococci in Cases of Chronic Rheumatic Cardiovalvular Disease (Montefiore and Bellevue Hospitals)*

Age, Years	Total No. of Cases	Green-Producing Streptococci					Indifferent Streptococci				
		Present	Absent	Predominating*	Not Predominating	Undetermined†	Present	Absent	Predominating*	Not Predominating	Undetermined†
14 and below....	75	75 (100%)	0	51 (68%)	7 (9%)	17 (23%)	70 (93%)	5 (7%)	0	70 (93%)	5 (7%)
15 to 29.....	21	21 (100%)	0	12 (57%)	0	9 (43%)	21 (100%)	0	0	19 (90%)	2 (10%)
30 and above...	39	39 (100%)	0	30 (77%)	4 (10%)	5 (13%)	39 (100%)	0	0	37 (95%)	2 (7%)
Total....	135	135 (100%)	0	93 (69%)	11 (8%)	31 (23%)	130 (96%)	5 (4%)	0	126 (93%)	9 (7%)

* More than 50 per cent of the total number of organisms in culture.

† In early cultures organisms were listed merely as present or absent.

ing from cardiac conditions other than chronic rheumatic cardiovalvular disease. In the normal group, in which there is a much smaller number of cases than in any of the other groups, there is a disproportionately large percentage of cultures showing over 50 per cent of hemolytic streptococci. These cultures were all taken from one person. Because of the hemolytic streptococci in her throat, more repeat cultures were taken from her than from any of the other normal controls. This accounts for the unusually high percentage. To determine whether hemolytic streptococci would appear in greater abundance in the throat flora of subjects with active rheumatic fever than in the throat flora of those with chronic cases, our data were again analyzed. The results remained essentially the same as those already recorded. For example, in 54 per cent of the cultures hemolytic streptococci constituted from 1 to 10 per cent of the flora. This contrasted with 59 per cent when

the entire group of cases of rheumatic fever was considered. In the other divisions the percentages were about the same.

Data on the incidence and preponderance of nonhemolytic streptococci in cases of rheumatic fever and in cultures are presented in tables 5 and 6. A number of cases and cultures are listed as "undetermined." This is due to the fact that at the beginning of our study green-producing and indifferent streptococci were recorded merely as present or absent. In some of the cases that were followed for a long period, cultures at one time might show a preponderance of green-producing streptococci and at another time a preponderance of indifferent streptococci. These cases were likewise listed in the "undetermined" column. Green-pro-

TABLE 6.—Incidence and Preponderance of Green-Producing and Indifferent Streptococci in Throat Cultures of Patients with Chronic Rheumatic Cardiovalvular Disease (Montefiore and Bellevue Hospitals)

Age, Years	Total No. of Cultures	Green-Producing Streptococci					Indifferent Streptococci				
		Present	Absent	Predominating*	Not Predomi- nating	Undetermined†	Present	Absent	Predominating*	Not Predomi- nating	Undetermined†
14 and below....	313	310 (99%)	3 (1%)	231 (74%)	53 (17%)	29 (9%)	263 (86%)	45 (14%)	3 (1%)	282 (90%)	28 (9%)
15 to 29.....	79	79 (100%)	0	54 (68%)	19 (24%)	6 (8%)	71 (90%)	8 (10%)	5 (6%)	63 (80%)	11 (14%)
30 and above...	80	80 (100%)	0	62 (78%)	12 (15%)	6 (7%)	78 (98%)	2 (2%)	5 (6%)	69 (86%)	6 (8%)
Total.....	472	469 (99%)	3 (1%)	347 (73%)	84 (18%)	41 (9%)	417 (88%)	55 (12%)	13 (3%)	414 (87%)	45 (10%)

* More than 50 per cent of the total number of organisms in culture.

† In early cultures organisms were listed merely as present or absent.

ducing streptococci were present in all the cases, and they predominated in 69 per cent. In 8 per cent of the cases they were not in the majority, and in 23 per cent their relative number was undetermined. Indifferent streptococci were present in 96 per cent of the cases, but they did not predominate in any. In 7 per cent the percentage of incidence was undetermined.

In tabulating the cultures, green-producing streptococci were present in 99 per cent and predominated in 73 per cent, while indifferent streptococci were present in 88 per cent and predominated in 3 per cent. In this connection it is interesting to note that Hitchcock,³⁴ in his studies on rheumatic and nonrheumatic patients at the hospital of the Rocke-

34. Hitchcock, C. H.: Studies on Indifferent Streptococci: Observations on Distribution of Indifferent Streptococci in Throats of Rheumatic and Non-Rheumatic Individuals, *J. Exper. Med.* 48:403, 1928.

feller Institute, found that 85 per cent carried indifferent streptococci in their throats. He believed that if repeated throat cultures were taken practically every person at some time or other would be found to harbor these organisms, even though they might be present in small numbers.

Many investigators have agreed that the majority of attacks or exacerbations of rheumatic fever are preceded by sore throat or by some infection of the upper respiratory tract. We attempted to ascertain if persons who were definitely known to have rheumatic fever have hemolytic streptococci associated with infections of the upper respiratory tract more frequently than do other persons. In tables 7, 8 and 9 data from Montefiore and Bellevue Hospitals are correlated which bear on this point.

In the light of previous investigations on the rôle played by the tonsils in first attacks and exacerbations of rheumatic fever, we divided our groups into subjects whose tonsils had not been removed and subjects on whom tonsillectomy had been performed. Sixty-one per cent of the patients with rheumatic fever from Montefiore Hospital and 27 per cent of the controls had had their tonsils removed. Seventy-two per cent of the cultures from the patients with rheumatic fever and 29 per cent of those from the controls were taken from throats in which there were no tonsils.

Throat cultures which yielded hemolytic streptococci at the time of an infection of the upper respiratory tract and which continued to show these organisms after the infection had subsided are grouped as infections of the upper respiratory tract caused by hemolytic streptococci. Four relationships have been tabulated: infection of the upper respiratory tract in which hemolytic streptococci are found; infection of the upper respiratory tract in which hemolytic streptococci are not found; absence of an infection of the upper respiratory tract, with the presence of *Streptococcus haemolyticus*, and absence of an infection of the upper respiratory tract, with the absence of *Streptococcus haemolyticus*. The analyses were made on the basis of the total number of throat cultures and subjects.

Relatively few patients in any of the diagnostic groups at Montefiore Hospital suffered from infections of the upper respiratory tract, and in these cases the majority of throat cultures showed no hemolytic streptococci (table 7). Of the 70 throat cultures taken from rheumatic patients during infections of the upper respiratory tract, 26 (37 per cent) showed hemolytic streptococci, while 44 (63 per cent) did not. Eleven throat cultures (61 per cent) from patients suffering from other cardiac conditions showed *Streptococcus haemolyticus* associated with infection of the upper respiratory tract, while 7 (39 per cent) did not. Analyses of cultures from subjects suffering from diseases unrelated to the ones just mentioned or from normal persons showed higher per-

TABLE 7.—*Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci in Throat Cultures (Montefiore Hospital) **

Group	Age, Years	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
Chronic rheumatic cardiorhvalvular disease	1-14	2	13	15 (39%)	3	20	23 (61%)	16	26	42 (22%)	23	128	151 (73%)
	15-29	..	7	7 (41%)	2	8	10 (59%)	3	5	8 (13%)	8	46	54 (87%)
	30 +	..	3	4 (27%)†	8	3	11 (73%)	9	1	10 (15%)	32	20	54 (83%)
Total.....		2	23	26 (37%)	13	31	44 (63%)	28	32	60 (19%)	63	191	259 (81%)
Arthritis.....	1-14
	15-29	2	2 (100%)
	30 +	5	1	6 (100%)
Total.....		5	3	8 (100%)
Other cardiac conditions	1-14	3	..	3 (100%)	1	1 (100%)
	15-29	1	1	2 (100%)	1	..	1 (3%)	4	12	18 (93%)†
	30 +	8	..	8 (62%)	5	..	5 (38%)	35	4	39 (27%)	82	21	106 (73%)§
Total.....		11	..	11 (61%)	6	1	7 (39%)	36	5	41 (25%)	86	33	124 (75%)
Other conditions	1-14	4	2	6 (30%)	..	1	1 (14%)	1	5	6 (17%)	15	15	30 (83%)
	15-29	1	1	1 (6%)	..	16	16 (94%)
	30 +	3	1	4 (100%)	14	2	16 (25%)	37	8	48 (74%)§
Total.....		4	2	6 (55%)	3	2	5 (47%)	15	8	23 (19%)	52	39	94 (80%)
Normal persons	1-14
	15-29	4	..	4 (80%)	1	..	1 (20%)	1	..	1 (9%)	6	4	10 (91%)
	30 +	1	1 (100%)
Total.....		4	..	4 (80%)	1	..	1 (20%)	1	..	1 (8%)	6	5	11 (92%)

* Records as to the presence of the tonsils are incomplete.

† For one culture.

‡ For two cultures.

§ For three cultures.

|| One culture showed no growth.

TABLE 8.—Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci in Throats (Montefiore Hospital) *

Group	Age, Years	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
Chronic rheumatic cardiovascular disease	1-14	2	6	8 (36%)	2	12	14 (64%)	6	14	20 (34%)	11	28	39 (66%)
	15-29	..	3	3 (25%)	2	7	9 (75%)	2	2	4 (17%)	3	16	19 (83%)
	30 +	..	1	2 (25%)†	4	2	6 (75%)	8	2	10 (25%)	18	14	33 (77%)†
Total.....		2	10	13 (31%)	8	21	29 (69%)	16	18	34 (27%)	32	53	91 (73%)
Arthritis.....	1-14
	15-29	1	1 (100%)
	30 +	4	1	5 (100%)
Total.....		4	2	6 (100%)
Other cardiac conditions	1-14	1	..	1 (100%)	..	1	2 (100%)	..	1	1 (100%)	..	3	6 (86%)†
	15-29	6	..	6 (67%)	22	3	25 (29%)	45	13	60 (71%)†
	30 +	3	..	3 (33%)
Total.....		4	..	4 (25%)	7	1	8 (75%)	23	4	27 (29%)	47	16	66 (71%)
Other conditions	1-14	3	1	4 (80%)	..	1	1 (20%)	1	2	3 (18%)	6	8	14 (82%)
	15-29	3	..	3 (100%)	..	1	1 (13%)	..	7	7 (87%)
	30 +	8	2	10 (25%)§	23	4	30 (75%)§
Total.....		3	1	4 (50%)	3	1	4 (50%)	9	5	14 (32%)	29	19	51 (78%)
Normal persons	1-14
	15-29	1	..	1 (50%)	1	..	1 (9%)	6	4	10 (91%)
	30 +	1	1 (100%)
Total.....		1	..	1 (50%)	1	..	1 (50%)	1	..	1 (8%)	6	5	11 (92%)

* Records as to the presence of the tonsils are incomplete.

† For one case.

‡ For two cases.

§ For three cases.

TABLE 9.—*Association of Infection of the Upper Respiratory Tract with Hemolytic Streptococci (Bellevue Hospital) **

Age, Years	Group	Infection of Upper Respiratory Tract						No Infection of Upper Respiratory Tract					
		Hemolytic Streptococci Present			Hemolytic Streptococci Absent			Hemolytic Streptococci Present			Hemolytic Streptococci Absent		
		Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total	Tonsils In	Tonsils Out	Total
		CASES											
1 to 14	Chronic rheumatic car- diovalvular disease.....	5	4	9 (31%)	1	3	4 (69%)	5	7	12 (33%)	8	10	24 (67%)
	Chorea.....	3	1	4 (29%)	2	8	10 (71%)
	Other cardiac conditions	1	2	3 (100%)
	Other conditions.....	3	..	3 (75%)	..	1	1 (25%)	3	..	3 (60%)	1	..	2 (40%)†
	Total.....	8	4	12 (71%)	1	4	5 (29%)	11	8	19 (33%)	12	20	39 (67%)
CULTURES													
1 to 14	Chronic rheumatic car- diovalvular disease.....	9	6	15 (70%)	1	3	4 (21%)	5	11	16 (35%)	11	30	47 (75%)
	Chorea.....	3	1	4 (24%)	2	11	13 (76%)
	Other cardiac conditions	1	4	5 (100%)
	Other conditions.....	3	..	3 (75%)	..	1	1 (25%)	3	..	3 (60%)	1	..	2 (40%)†
	Total.....	12	6	18 (78%)	1	4	5 (22%)	11	12	23 (36%)	15	51	67 (74%)

* Records as to the presence of the tonsils are incomplete.

† For one culture.

centages than those of the rheumatic fever group. From tables 7 and 8 it appears that the younger subjects (those below 15 years and those between 15 and 29 years) had hemolytic streptococcic infections of the throat more frequently than did those above the age of 30. Thirty-six per cent of the rheumatic patients between 1 and 14 years of age, 25 per cent between 15 and 29 and 25 per cent above 30 gave cultures which were positive for hemolytic streptococci during an infection of the upper respiratory tract. Approximately the same percentage of cases was found in the group from Bellevue Hospital. Here all the patients were under 15 years of age, and 31 per cent of them gave hemolytic streptococcus cultures at the time they had an infection of the upper respiratory tract. The percentage of positive throat cultures in these two groups, however, showed wide variance. In the group from Montefiore Hospital it was 39 per cent, whereas in the group from Bellevue Hospital it was 79 per cent. It may be that these differences in the percentages are partly accounted for by the disproportion of tonsillectomies in these two institutions. Many more of the patients in Montefiore Hospital had had their tonsils removed. Among the patients with rheumatic fever at Montefiore Hospital below the age of 15 who had not had their tonsils removed, 18 out of 44 (41 per cent) gave cultures that showed hemolytic streptococci, whereas among those who had no tonsils only 39 of a total of 187 (21 per cent) gave positive cultures. The fact that the tonsils were present in the majority of controls may also be a factor in accounting for the high percentages among these groups.

Analyses of the data during periods when there were no involvements of the upper respiratory tract show that hemolytic streptococci were absent in the majority of throat cultures (table 7). It is impossible to observe any tendency for them to be found with greater frequency in the throat cultures of patients with rheumatic fever than in those of other persons. As in the case of those suffering from infection of the upper respiratory tract (table 8), hemolytic streptococci were found more frequently in the throats of the younger subjects.

We now arrive at the final question: Is there a definite relationship between exacerbations of rheumatic fever and previous infections of the upper respiratory tract with *Streptococcus haemolyticus*? Table 10 summarizes the findings.

The number of patients with rheumatic fever at Montefiore Hospital considered in this report is 101, but only 96 are included in the present analysis, as the data for 5 patients are too indefinite to be tabulated. Thirty patients had only 1 throat culture, but 29 of these suffered no relapse during the investigation. For 9 patients more than one relationship is recorded. In determining whether a recrudescence occurred in a patient, the following clinical symptoms were considered: rise in

temperature, marked increase in pulse rate, electrocardiographic changes, and the appearance of rheumatic nodules, purpura, polyarthritides or chorea.

Thirty-seven patients had exacerbations. Of this number, 18 suffered from an infection of the upper respiratory tract about fifteen to twenty-one days prior to a recrudescence of the rheumatic symptoms, while 19 had no recognizable inflammatory condition of the throat. It appears that exacerbations occur as frequently when there has been no infection of the throat as when one has been present. However, of the 37 patients who experienced recrudescences, 23 (62 per cent) showed throat cultures which were positive for hemolytic streptococci some three weeks or more prior to the relapse; 14 (38 per cent) had

TABLE 10.—*Relation of Infection of Upper Respiratory Tract and Hemolytic Streptococcal Infection to Exacerbations in Patients with Rheumatic Fever*

	Hemolytic Streptococci		No Hemolytic Streptococci		Total	
	Exacer- bations	No Exacer- bations	Exacer- bations	No Exacer- bations	Exacer- bations	No Exacer- bations
Montefiore Hospital						
Infection of upper respir- atory tract.....	9	10	9	13	18	23
No infection of upper respiratory tract....	14	11	5	41	19	52
Total.....	23	21	14	54	37	75
Bellevue Hospital						
Infection of upper respir- atory tract.....	2	3	1	0	3	3
No infection of upper respiratory tract.....	7	3	4	8	11	11
Total.....	9	6	5	8	14	14

no known occurrence of these organisms, although 9 patients did experience an infection of the upper respiratory tract. Whether the 9 subjects who had an infection of the upper respiratory tract in which *Streptococcus haemolyticus* was not the causative agent would have shown these organisms had more cultures been taken at the time of the infection is an open question. All throat cultures were secured within from twenty-four hours to five days after the onset of the infection. Coburn and Pauli³ noticed that *Streptococcus haemolyticus* usually disappeared from the throat flora within two weeks. If this organism had been the causative agent of these infections it is probable that the cultures would have yielded it, even though its proportion to the total throat flora might have been greatly reduced. There is still another factor to be borne in mind. A great number of these patients were children, and it is not unlikely that some of them had mild colds which caused very few symptoms and which were either not observed

or not recorded. Five of the patients who had exacerbations showed neither an infection of the upper respiratory tract nor a throat culture which was positive for the hemolytic streptococcus preceding the attack. Thus it is seen that of the 37 patients who suffered exacerbations of symptoms, 32 had a definite history of either an infection of the upper respiratory tract or the presence of hemolytic streptococci or both, preceding the attack.

Seventy-five patients were free from recrudescence. In 54 (72 per cent), hemolytic streptococci did not constitute a part of the throat flora during any of the periods when cultures were taken. The majority of these (41 patients) did not experience an acute condition of the upper respiratory tract. However, 21 subjects (28 per cent) did have throat cultures which were positive for the hemolytic streptococcus without any following exacerbation. But this number is small in comparison with the number who had exacerbations following *Streptococcus haemolyticus* infections.

In about two thirds of the patients with rheumatic fever the exacerbations of symptoms were associated with previous *Streptococcus haemolyticus* infections, and, roughly, the same proportion of the patients who had no exacerbations did not have this organism in their throat cultures, but for the remaining one-third in each group there is a contradictory and as yet undetermined relationship. The data from Bellevue Hospital substantiate these findings. On the whole, these results apparently confirm those of Coburn and Pauli and of other investigators who believed that there is a definite relationship between the presence of *Streptococcus haemolyticus* in the upper respiratory tract and an exacerbation of rheumatic symptoms within from fifteen to twenty-one days later.

SUMMARY AND CONCLUSIONS

The present investigation includes 321 cases and 840 cultures from Montefiore and Bellevue Hospitals, New York City. Forty-six per cent of the subjects were patients with rheumatic fever. Fifty-eight per cent of the cultures were taken from this group. The remainder were taken from normal persons and from patients suffering from diseases other than rheumatic fever; these constituted the control group. In more than one third of the cases of rheumatic fever and in more than one half of the cultures taken from this group the patients were under 15 years of age.

1. In making cultures of hemolytic streptococci, it seems that rabbit blood is slightly better than horse blood. However, if appropriate dilutions are made, equally good results can be obtained with horse blood.

2. The percentage of cultures which were positive for the hemolytic streptococcus taken from the throats of patients with rheumatic fever was approximately the same as that found in other persons.

3. In these positive cultures, the hemolytic streptococcus appeared to be no more abundant in those obtained from patients with rheumatic fever than in those from other persons.

4. Throat cultures of patients with rheumatic fever taken during an infection of the upper respiratory tract showed no greater incidence of hemolytic streptococci than those from other persons who were suffering from a cold or from sore throat.

5. Infections of the upper respiratory tract were found associated with *Streptococcus haemolyticus* more frequently in young persons who were suffering from rheumatic fever than in older patients with this disease.

6. Hemolytic streptococci were found more frequently associated with infection of the upper respiratory tract in rheumatic persons who had not had their tonsils removed than in those on whom tonsillectomy had been performed.

7. Green-producing streptococci were present in all the cases and in 99 per cent of the cultures. They predominated in 69 per cent of the cases and in 73 per cent of the cultures.

8. Indifferent streptococci were present in 96 per cent of the cases and in 88 per cent of the cultures. They predominated in 3 per cent of the cultures.

9. In the groups studied, exacerbations of acute rheumatic fever occurred as frequently when there was no infection of the throat as when there was.

10. The fact that the majority of those in whom exacerbations of rheumatic fever occurred were persons who had hemolytic streptococci in their throats suggests a possible relationship between this organism and the reappearance of the symptoms.

Dr. B. B. Oppenheimer, Director of the Medical Service, Montefiore Hospital, and Dr. W. H. Park, Director of the Bacteriologic Laboratories of New York University and Bellevue Hospital Medical College, offered helpful suggestions in the course of this work.

Book Reviews

Chronic Nephritis and Lead Poisoning. By L. J. Jarvis Nye, M.B., Ch.M. Cloth. Price, 12 shillings, six pence. Pp. 145. Sydney, Australia: Angus & Robertson, Ltd., 1933.

This interesting monograph is based on the author's careful etiologic study of a type of chronic nephritis occurring among the children and young adults of Queensland, the prevalence of which is out of proportion to that observed in the other states of Australia.

The work is a distinct addition to the present knowledge of plumbism in that it establishes a definite relationship between the constant ingestion of lead and the well known signs of intoxication and late sequelae in the form of a chronic vascular type of Bright's disease. Nye shows logically that the usual known causes of chronic nephritis do not operate in the tropical climate of Queensland; streptococcic infections are relatively rare. On the other hand, he establishes a convincing association with lead poisoning acquired earlier in a large proportion of the cases cited. Lead paint, altered to scaly or powdery forms of the carbonate as the result of exposure to the tropical sun, is shown to be the essential source. Careful investigation into the early lives of the children studied brought out important facts in regard to most of them. They lived in the common type of frame house with wide verandas which showed disintegrating paint. Some were in the habit of licking the rain-drops from the railings of the veranda, and nearly all were either thumb-suckers or nail-biters or both. Since they lived out of doors much of the time, their hands were frequently contaminated, and absorption was by the gastro-intestinal route.

The criteria for the diagnosis of plumbism are satisfactory, and the subject matter is well arranged. Several chapters are of special interest, particularly those on the source of lead and on the relationship of lead poisoning to renal disease. Unfortunately, the pathologic presentation which the reader looks forward to is wanting, and the interest which the careful etiologic study has aroused is left suspended because of the lack of pathologic data. Perhaps more will be written on this phase of the subject later. The clinical descriptions and records of cases are good, but the correlation of the various manifestations appears to have been difficult, as it frequently is in Bright's disease.

Interest is naturally revived in speculation as to the possible etiologic relationship of lead to some of the severe types of vascular hypertension and nephritis seen in younger persons in the United States and elsewhere.

A Text-Book of Medicine. By 141 American authors. Edited by Russell L. Cecil, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital, New York City, and Foster Kennedy, M.D., F.R.S.E., Associate Editor, Diseases of the Nervous System; Professor of Neurology, Cornell University Medical College; Director, Department of Neurology, Bellevue Hospital, New York City. Third edition, revised and entirely reset. Cloth. Price, \$9. Pp. 1,664, with 14 illustrations. Philadelphia: W. B. Saunders Company, 1933.

It seems obvious that the question confronting the writer of a textbook of medicine is not what shall be included in the work but what shall be left out. This work covers the field of medicine about as well as it is possible to do in a single volume. Indeed, no little ingenuity is required to compress so much information into a single book, and the editor is to be congratulated on his success in the undertaking.

Dr. Cecil states in his prefatory remarks that the task of writing a textbook of medicine today could not be satisfactorily accomplished by a single author. One

wonders if this statement might not be argued. There is a certain smoothness of style in a book by a single author that is necessarily absent when a multiplicity of authors is at work. Perhaps, however, the medical student of today has a more agile mind than his predecessor. So far as information is concerned, it is difficult to imagine a more informative book than some of the works of the past by single authors.

After all, each important subject in a textbook of medicine must be considered as an abstract of material from which an additional textbook might be written. There is reason to suspect, at least, that a more suitable abstract might be written by a man with broad general knowledge and experience than by the expert whose knowledge is more or less limited to a single field.

Whatever the opinion on single or multiple authorship, the student and practitioner will find the present work equal to any reasonable demand made on it. It is without a superior in its field today.

Klassifikation der Schizomyceten (Bakterien): Versuch einer wissenschaftlichen Klassifikation der Bakterien auf botanischer Grundlage. By Prof. Dr. Ernst Pribram. Price, 8 marks. Pp. 142. Vienna: Franz Deuticke, 1933.

The appearance of this work emphasizes the fact that a suitable and more or less satisfactory classification of bacteria is still lacking.

Pribram attempts to classify bacteria on a scientific basis, as in botany. He also attempts to apply the nomenclature of an international codex of botanic nomenclature, with the view to its practical application. This new classification and nomenclature, he hopes, will facilitate the study of bacteria and will also prove to be more practical than the system now in use. Study of the work shows what labor and time he has expended; this can be appreciated only by a scholar who has the time and interest to read the book.

With due respect to Pribram's wide experience and knowledge, which in themselves guarantee the value of the work, there are certain points that may invite some criticism, which he has foreseen. In the attempt to simplify the classification of bacteria portions have been overdone. Sometimes the important characteristics of bacteria are overlooked. One example is the grouping of *Pasteurella*, *Brucella*, *Hemophilus* and *Neisseria* in the same family.

The scientific nomenclature of Pribram's work is overshadowed by a liberal use of proper names, particularly the name of the author. It is questionable, at least among the majority of bacteriologists, whether the mere renaming of a genus, family or other class should be accompanied by the author's name.

As is stated by Pribram, the work is an outgrowth of a classification of Kral's bacteriologic collection (which at present is owned by Pribram). It may serve well as a descriptive catalog for the collection, but it is not a suitable book for laboratories or schools.

Tratado de la diabetes. By Professor Pedro Escudero. Second edition. Price, \$15. Pp. 1,001. Buenos Aires: El Ateneo, 1933.

What Joslin's treatise is to English-speaking physicians Escudero's is to the Spanish, that is, a standard authoritative guide for the treatment of diabetes. The second edition is practically a new work; according to the author, there is not a page that has not been revised or modified. This revision, he points out somewhat platitudinously, was necessitated by the fact that the majority of concepts have been modified, clarified or proved, that medicine is a science in constant evolution, and that what appeared obvious yesterday is erroneous today, the impossible of other days becoming axiomatic.

The creation of the Municipal Institute of Diseases of Nutrition has made it possible for the author and his co-workers to study thousands of new cases of diabetes within the past five years. This opportunity has been tremendously important, because "the study of diabetes is the small and brilliant spot in the

firmament of diseases of nutrition and it has succeeded in orienting the study of all the nutritional diseases." Constant investigation has been in progress at the institute, and the following investigators have made many valuable contributions: Schultz Ortiz, Boscq, Orosco, Peco, Gravano, Ferradas, Casanegra, Landabure, Puchulu, Secco, Miranda Gallino, Izzo, Pangaro, Silvestri, Tobias and Silvestri.

"This book," he states in the preface, "is not a synthesis of foreign ideas filtered through our experience; it is the embodiment of doctrine, supported by the men who form our school and who look for its constant betterment by unending and honest investigation."

Handbook of Chemotherapy. Part I: Metal-Free Organic Compounds.

By Dr. Viktor Fischl and Dr. Hans Schlossberger. Translated from the German by D. A. S. Schwartzman. Price, \$8. Baltimore: H. G. Roebuck & Son, 1933.

This handbook represents the collaboration of a chemist and a physician. It contains therefore, detailed accounts of the chemistry of therapeutic preparations with which it deals and the opinions of the physician on the clinical results of their use. This volume is devoted to metal-free organic compounds. These are divided into eleven groups: acyclic chlorine compounds; unsaturated fatty acids; simple derivatives of benzene and naphthalene, oxy and oxo compounds; amino-acids; derivatives of quinoline (with the exception of quinine) and similar substances; quinine and its derivatives; emetine and its derivatives; the other plant substances; derivatives of acridine; the other dyestuffs, and colorless derivatives of urea.

In the discussion of such recognized chemotherapeutic agents as quinine and chaulmoogra oil, a splendid historical account of their early empirical use is given, with a satisfactory discussion of their method of action, presented in an unprejudiced manner. The same method of approach is employed in presenting the other agents. Each chapter has a complete bibliography. The volume is well translated, and the subject matter is presented clearly and concisely. This book has a place in medical literature, as it contains a large amount of information which is ordinarily not readily accessible.

Traité de physiologie normale et pathologique: Tome I: Physiologie générale. Published under the direction of G. H. Roger and Léon Binet. Price, 165 francs. Pp. 1,136, with 95 illustrations. Paris: Masson & Cie, 1933.

Although this is the first volume of an extensive work which began to appear in 1927, it is among the last volumes to be finished; all but one of the eleven volumes are off the press, and the preparation of a second edition of volumes VII and XI is announced. Each volume is complete in itself and deals with a definite division of normal and pathologic physiology. The editors have had the aid of a large number of collaborators, and the subdivisions of the subject matter of each volume are treated by various authors. This volume of 1,136 pages, the largest so far issued, deals with the following topics: the general properties of living matter, general cellular physiology, tissue culture, physical chemistry of the cells, cellular constitution, the action of physical agents. (pressure, radiant energy and electricity), the action of roentgen rays and of radioactive substances, toxins, ferments and venoms. The book is essentially one of reference, the main facts of physiology being given together with much of the recent literature. It would seem to be of value chiefly to French scientists.

INFECTIONS WITH PNEUMOCOCCUS TYPE III AND TYPE VIII

CHARACTERIZATION OF PNEUMONIA CAUSED BY PNEUMOCOCCUS
TYPE III AND THAT ASSOCIATED WITH A BIOLOGICALLY CLOSELY
RELATED ORGANISM, PNEUMOCOCCUS TYPE VIII

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The classification of pneumococci into serologically specific types¹ has rendered possible a thorough study of the distribution of these organisms in health and in disease. The investigation had its inception in relation to lobar pneumonia, but it soon became apparent that this clinical entity comprises a group of specific infectious diseases, alike in their clinical and anatomic manifestations but differing etiologically.² The significance of this distinction between the etiologic, as contrasted with the clinico-anatomic, classification has become increasingly important with the advent of serum therapy, which thus far has been shown to be strictly type specific in its action.

Furthermore, this consciousness of the responsible bacterial incitant has indicated that the reverse is also true; that is, the same organism, belonging to the same serologic type, may give rise to different clinical pictures in different persons. The latter fact is not emphasized as frequently as the former, because most writers have been interested primarily in lobar pneumonia. When, however, the disease picture associated with each type of pneumococcus is studied, it becomes clear that the

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. (a) Dochez, A. R., and Gillespie, L. J.: A Biological Classification of Pneumococci by Means of Immunity Reactions, *J. A. M. A.* **61**:727 (Sept. 6) 1913. (b) Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antisera for Those Types, *J. Exper. Med.* **55**:531 (April) 1932.

2. Cole, R.: Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1928.

different types vary in the uniformity with which they produce lobar pneumonia, "atypical" pneumonia or bronchopneumonia or focal infections without pneumonia. Epidemiologic investigations³ and bacteriologic studies in a variety of cases without or with other pulmonary diseases have also indicated wide variations in the frequency with which the various types of pneumococci occur without demonstrable relation to disease.⁴ Cole² and more recently Gundel⁵ have emphasized the uniformity with which types I and II are associated with primary lobar pneumonia. Most of the other types are less uniform in the character of the disease that they produce.^{4a} Types III and VIII, with which this paper is concerned, are notable examples of types which are not associated with a uniform clinico-anatomic disease.

The type III pneumococcus has a number of distinctive bacteriologic, immunologic and epidemiologic features. Because of its large capsule and its tendency to grow in chains and produce a large mucoid colony on the surface of enriched solid mediums, it has been known variously as "*Streptococcus capsulatus*," "*Streptococcus mucosus*" and "*Pneumococcus mucosus*." An organism of this description was early recognized in spontaneous diseases in animals.⁶ In man, it was isolated first from a case of meningitis⁷ and then from other inflammatory lesions.⁸ Its

3. Stillman, E. G.: Further Studies on the Epidemiology of Lobar Pneumonia, *J. Exper. Med.* **26**:513 (Oct.) 1917. Rosenau, M. J.; Felton, L. D., and Atwater, R. M.: An Epidemiologic Study of Pneumonia and Its Mode of Spread, *Am. J. Hyg.* **6**:463 (May) 1926. Powell, J. P.; Atwater, R. M., and Felton, L. D.: The Epidemiology of Pneumonia, *Am. J. Hyg.* **6**:570 (July) 1926. Webster, L. T., and Hughes, T. P.: Incidence and Spread of Pneumococci in Nasal Passages and Throats of Healthy Persons, *J. Exper. Med.* **53**:535 (April) 1931. Gundel, M.: Bakteriologie und epidemiologische Untersuchungen über die Besiedlung der oberen Atmungswege Gesunder mit Pneumokokken, *Ztschr. f. Hyg. u. Infektionskr.* **114**:659, 1933. Smillie, W. G.: The Epidemiology of Lobar Pneumonia: A Study of the Prevalence of Specific Strains of Pneumococci in the Nasopharynx of Immediate Family Contacts, *J. A. M. A.* **101**:1281 (Oct. 31) 1933.

4. (a) Sutliff, W. D., and Finland, M.: The Significance of the Newly Classified Types of Pneumococci in Disease: Types IV to XX Inclusive, *J. A. M. A.* **101**:1289 (Oct. 31) 1933. (b) Cooper et al.^{1b}

5. Gundel, M.: Die Bakteriologie, Epidemiologie, und spezifische Therapie der Pneumokokken-Infektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, *Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap.* **12**:129, 1931.

6. Poels, J., and Nolen, W.: Das Contagium der Lungenseuche, *Fortschr. d. Med.* **4**:217, 1886. Benaghi, R.: Ueber einen *Streptococcus capsulatus*, *Centralbl. f. Bakt. (Abt. 1)* **22**:273, 1897.

7. Bonome, A.: Zur Aetiologie der Meningitis cerebro-spinalis epidemica, *Beitr. z. path. Anat. u. z. allg. Path.* **8**:377, 1890.

8. Atkinson, R. T.: A Pathogenic Diplococcus, *J. Boston Soc. M. Sc.* **1**:2, 1897. Howard, W. T., and Perkins, R. C.: *Streptococcus Mucosus* (Nov. Spec.?) Pathogenic for Man and Animals, *J. M. Research* **6**:163, 1901.

association with human lobar pneumonia was first reported by Richardson,⁹ who recovered it at autopsy from the lungs in four typical cases. Schottmüller¹⁰ described seven human strains of this organism: one from the pus of a postpartum endometrial abscess, one from the blood and pus in a case of perforative peritonitis, three from the pus in cases of purulent meningitis, one from the blood in a case of pyelephlebitis and one from the blood in a case of croupous pneumonia.

When obtained from fresh exudate this organism usually has a much larger capsule than other pneumococci. It excretes larger amounts of its soluble specific carbohydrate into the medium in which it grows.¹¹ Thus far, it has been found impossible to produce with this organism in animals specific protective antibodies of high titer.¹² Other immunologic reactions of animals to the type III pneumococcus have also been found to be different from those observed with types I and II.¹³ Type III is the most common type of pneumococcus found in the normal nasopharynx and in persons with chronic infections of the respiratory tract or of the middle ear.¹⁴

In relation to the etiology of pneumonia, type III usually ranks third or, with some authors, second among the various types of pneumococci. It may cause as high as 20 per cent of cases of pneumococcic pneumonia (Blake¹⁵). Cecil, Baldwin and Larsen¹⁶ and more recently Blake¹⁵ have brought out a number of the more important features of

9. Richardson, O.: Pseudo-Pneumococci in Lobar Pneumonia, J. Boston Soc. M. Sc. 5:499, 1901.

10. Schottmüller, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr. 50:908, 1903.

11. Dochez, A. R., and Avery, O. T.: The Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. 26:477 (Oct.) 1917.

12. Wadsworth, A. B., and Kirkbride, M. B.: A Note on the Production of Antipneumococcus Sera, J. Exper. Med. 25:629 (May) 1917.

13. Hanes, I. M.: An Immunological Study of Pneumococcus Mucosus, J. Exper. Med. 19:38 (Jan.) 1914. Singer, E., and Adler, H.: Immunität gegen Pneumococcus Typus III, Ztschr. f. Immunitätsforsch. u. exper. Therap. 41:71, 1924. Tillett, W. S.: Studies on Immunity to Pneumococcus Mucosus (Type III), J. Exper. Med. 45:713 and 1093, 1927; 46:434, 1927.

14. (a) Gundel, M., and Linden, H.: Bakteriologische Untersuchungen an Leichenlungen unter besonderer Berücksichtigung ihrer Bedeutung für das Pneumonieproblem, Ztschr. f. Hyg. u. Infektionskr. 112:41, 1931. (b) Wirth, E.: Der Erreger der akuten Mittelohrentzündung. Beitrag zur Bakteriologie des Streptococcus mucosus, Centralbl. f. Bakt. (Abt. 1) 98:501, 1926; Die Pneumokokkentypen in der Oto-Rhinologie, *ibid.* 102:40, 1927. (c) Footnote 3.

15. Blake, F. G.: Observations on Pneumococcus Type III Pneumonia, Ann. Int. Med. 5:673 (Dec.) 1931.

16. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia: A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. 40:253 (Sept.) 1927.

the cases of pneumonia associated with this type. These writers pointed out the high incidence in old persons and in persons with chronic debilitating disease as an explanation of the high mortality. Cecil, Baldwin and Larsen also called attention to the higher incidence among elderly women, to the somewhat longer duration of the disease and to the lesser frequency with which recovery by crisis takes place in pneumonia due to type III as compared with that due to other types of pneumococci.

The type VIII pneumococcus also has important features which make it of special importance. This type was first studied by Sugg and Harris as an atypical strain of type III.¹⁷ It is closely related immunologically to type III and in routine typing can be readily confused with the latter because of the high degree of cross-agglutination which may occur in some typing serums.^{1b} In a recent study in this laboratory,¹⁸ cross-agglutination and the capacity for cross-protection of mice were also found to exist in the serum of many human patients recovering from pneumonia associated with these two types of pneumococci. In relation to pneumonia, type VIII has been, in our experience,^{4a} the most frequent among the types recently separated from the pneumococci previously included in group IV.^{1b} It was early observed that the disease caused by this type differs significantly from that due to type III.

The forms of pneumonia caused by these two organisms have been chosen for presentation because they offer a number of features of special interest. They are encountered frequently. They give an interesting contrast with the disease associated with the two commonest types of pneumococci, namely, types I and II. The organisms have frequently been confused because of their cross-agglutination in the serums commonly used for typing. They are closely enough related chemically to cross-agglutinate and to produce high degrees of cross-protection in animals and in man, and yet they produce different disease pictures. The forms of pneumonia due to types I and II will be compared with those due to types III and VIII, and the differences between the forms caused by the latter types will be contrasted.

17. Sugg, J. Y.; Gaspari, E. L.; Fleming, W. L., and Neill, J. M.: Studies on Immunological Relationships Among the Pneumococci: I. A Virulent Strain of *Pneumococcus* Which Is Immunologically Related to but Not Identical with Typical Strains of Type III Pneumococci, *J. Exper. Med.* **47**:917 (June) 1928. Harris, A. L.; Sugg, J. Y., and Neill, J. M.: Studies on Immunological Relationship Among the Pneumococci: II. A Comparison of the Antibody Response of Mice and of Rabbits to Immunization with Typical Type III Pneumococci and to Immunization with a Related Strain, *ibid.* **47**:933 (June) 1928.

18. Finland, M., and Winkler, A. W.: Response to Infections with Antibody Type III and the Related Type VIII *Pneumococcus*, *J. Clin. Investigation* **13**:79 (Jan.) 1934.

PATIENTS STUDIED AND SOURCES OF PNEUMOCOCCI

During the period between Nov. 1, 1929, and May 20, 1933, about 2,000 patients were studied bacteriologically with particular reference to the presence of the various serologic types of pneumococci. In addition to typing serums of types I, II and III, there were available, through the kindness of Dr. William H. Park and Miss Georgia Cooper, serums for types IV to XX throughout the entire period and a total of thirty-two specific typing serums during the last year. Most of the pneumococci obtained during this period were typed with the available serums, and special attention was paid to the two serologically related pairs, types II and V and types III and VIII. Most of the patients had pneumonia or a disease simulating pneumonia. The remainder were patients from whom pneumococci were obtained from various sources in the regular bacteriologic laboratory. In the course of this study, type III pneumococci were obtained, on one or more occasions, from 282 patients, and type VIII, from 125 patients.

The bacteriologic methods have been described elsewhere.¹⁹ Briefly, all specimens of sputum were subjected to routine mouse typing,²⁰ and on most of them rapid typing was first carried out by the stained slide microscopic agglutination technic described by Sabin.²¹ Care was taken to differentiate between the type III and the type VIII organisms by agglutinating each strain in antiserums of both of these types and by repeating the agglutinations with greater dilutions of antiserum in many instances in which cross-agglutination was observed. In the cases of pneumonia an attempt was made to obtain several specimens of sputum and blood. Purulent exudates obtained during life and material obtained at autopsy were cultured.

The determination of the type of organism was made in 60 per cent of the cases of pneumonia from sputum alone, in 5 per cent from blood alone, in 14 per cent from autopsy material alone and in the remaining cases from two or from all three of these sources. The same proportions were found in both the type III and the type VIII cases. In general, all pneumococci obtained from the same patient, either from multiple specimens of the same material or from different materials, were of the same serologic type. A certain number of mixed infections with other types of pneumococci and with other organisms

19. Sutliff, W. D., and Finland, M.: Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), *J. A. M. A.* **96**:1465 (May 2) 1931.

20. Avery, O. T.; Chickering, H. T.; Cole, R. I., and Dochez, A. R.: *Acute Lobar Pneumonia*, New York, Rockefeller Institute for Medical Research, monograph 7, 1917.

21. Sabin, A. B.: The Microscopic Agglutination Test in Pneumonia, *J. Infect. Dis.* **46**:469 (June) 1930.

occurred (table 1). Space does not permit a detailed description of these cases. Many of them represented concurrent or consecutive infections. In most instances, however, one of the organisms probably had no relation to the disease.²² In cases of pneumonia, the type III pneumococcus was found to be associated with other significant organisms more frequently than any other type.

RELATION OF PNEUMOCOCCI OF TYPES III AND VIII TO PNEUMONIA
AND TO OTHER DISEASES

The present discussion is concerned primarily with the cases of pneumonia. For purposes of orientation and for comparison all the cases in which pneumococci of types III and VIII were obtained have been classified. An attempt was made to classify the cases of pneumonia according to the character of the pulmonary lesion. All cases

TABLE 1.—*Number of Patients with Type III and Type VIII Pneumonia in Whom Other Significant Organisms Were Obtained*

Organism	Type III Pneumonia	Type VIII Pneumonia
<i>Streptococcus haemolyticus</i>	8	4
<i>Staphylococcus aureus</i>	2	0
<i>Staphylococcus aureus</i> and <i>Streptococcus haemolyticus</i>	2	0
<i>Bacillus mucosus-capsulatus</i> (Friedländer).....	3	1
<i>Pneumococcus</i> type I.....	3	2
<i>Pneumococcus</i> type II.....	2	0
<i>Pneumococcus</i> type III.....	..	1
<i>Pneumococcus</i> types V, VIII, XI, XVII and XX (1 each).....	5	0
Total mixed infections.....	25	8

with homogeneous involvement were called lobar pneumonia, and those with patchy consolidation were termed bronchopneumonia. The clinical, roentgenologic and pathologic data were all utilized in making this distinction. In table 2 are shown the number and the percentage of patients from whom each type of organism was isolated who had (1) pneumonia of any kind or empyema, (2) bronchopneumonia, (3) purulent foci of infection without demonstrable pneumonia and (4) conditions showing no particular relation to either pneumonia or focal pneumococcic infection. Similar figures for pneumococci of types I and II are shown for comparison. Both the type III and the type VIII organisms showed a high incidence in cases of focal purulent infections, and both were found in more cases without pneumococcic disease than were types I and II. Furthermore, bronchopneumonia was rare both clinically and at autopsy among the patients from whom types I and II were isolated, whereas it was present in a large proportion of those from

22. Winkler, A. W., and Finland, M.: Antibody Response to Infection with the Newly Classified Types of Pneumococci (Cooper), *J. Clin. Investigation* **13**: 109 (Jan.) 1934.

whom types III and VIII (particularly the latter) were obtained. The discrepancy between the percentage of cases of bronchopneumonia caused by type VIII found clinically and the percentage found at autopsy is explicable on the basis of the much higher mortality from bronchopneumonia than from lobar pneumonia of this type. This is also true

TABLE 2.—*Relative Frequency with Which Type III and Type VIII Pneumococci Were Isolated from Patients With and Without Pneumonia (Types I and II Included for Comparison)*

Pneumococcus Type	Total Number of Patients	Pneumonia and Empyema		Broncho-pneumonia		Focal Infections		No Pneumococcal Disease	
		Number	Per Cent of Type	Number	Per Cent of Type	Number	Per Cent of Type	Number	Per Cent of Type
III	282	225	80	48	17	30	11	27	10
VIII	125	105	84	32	26	11	9	9	7
I	434	410	94	13	3	10	2	14	3
II	219	203	93	10	5	6	3	10	5
Cases with Autopsy									
III	72	64	89	18	22	5	7	3	4
VIII	27	21	78	13	48	3	11	3	11
I	71	67	94	8	11	0	0	4	6
II	36	31	86	3	8	2	6	3	8

TABLE 3.—*Number of Patients with Conditions Other Than Pneumonia from Whom Type III and Type VIII Pneumococci Were Obtained*

	Type III Pneumococcus		Type VIII Pneumococcus	
	Number of Patients	Deaths	Number of Patients	Deaths
Chronic pulmonary diseases.....	13	3	2	2
Infections of upper respiratory tract.....	7	0	2	0
No respiratory disease.....	5	1	1	0
Bacteremia (source unknown).....	2	2	4	0
Total nonpneumococcal diseases.....	27	6	9	2
Otitis media and mastoiditis.....	15	1	1	0
Meningitis	4	4	3	3
Peritonitis	4	1	4	3
Other purulent foci.....	7	2	3	0
Total focal infections.....	30	8	11	6
Total conditions other than pneumonia..	57	14	20	8

of type I and type II bronchopneumonia but not of type III, as will appear later.

All of the cases of nonpneumonic conditions, including those without demonstrable pneumococcal infections and those with focal infections, are classified in table 3. The high incidence of infections of the middle ear or mastoid with type III pneumococci, also mentioned by others,^{14b} is worthy of note, as is the frequency with which this type of pneumococcus is found in persons with respiratory infections of various kinds.

The remainder of this paper will deal only with the cases in which pulmonary consolidation was found. There were in all 225 cases of type III pneumococcic pneumonia and 105 of type VIII. The condition was fatal in 135 of the former group (a mortality of 60 per cent) and in 38 of the latter group (a mortality of 36 per cent).

RELATION OF AGE TO INCIDENCE AND MORTALITY

In chart 1 are represented the number of patients in each age group who recovered and the number who died. The increasing mortality with advancing age is apparent with both types of pneumonia. The more frequent occurrence of type III pneumonia in the older age groups is at

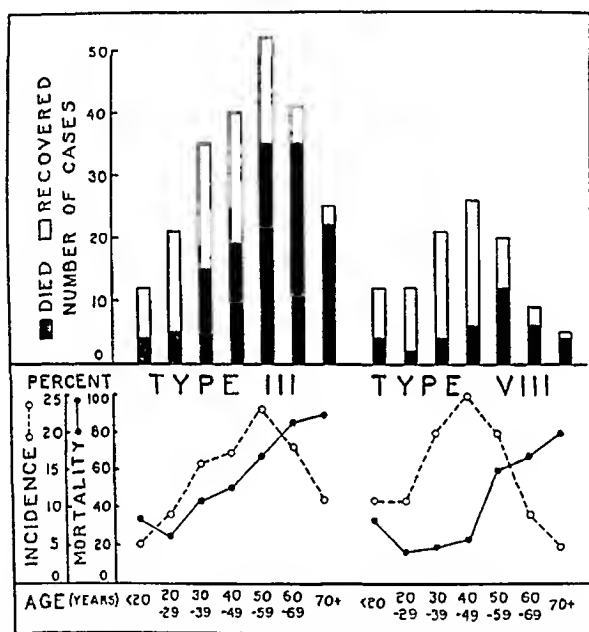


Chart 1.—Percentage incidence and mortality of type III and type VIII pneumonia.

once apparent. The highest incidence of this type was in persons between 40 and 69, 58 per cent of all the patients being of this age group and 11 per cent 70 or older. Among the patients with type VIII pneumonia, 64 per cent were between 30 and 59, and 14 per cent were 60 or older.

In chart 2, the age distribution of the cases of each of these types and also of those of types I and II are plotted together, and the mortality by age groups is similarly shown. From this chart it appears that there is a smaller percentage of younger and a greater percentage of older patients with type III pneumonia than with any of the other types. Pneumonia of types I and II affects the highest percentage of young patients and the fewest old ones, and type VIII pneumonia has an inter-

mediate age distribution. The mortality was found to be lower for type VIII pneumonia in persons of all ages except under 20 years. The mortality from type III pneumonia was higher in most age periods. The mortality from type III pneumonia was similar to that from type II, and type VIII pneumonia caused a mortality similar, in most age periods, to that of type I.

RELATION OF SEX TO INCIDENCE AND MORTALITY

Pneumonia of all kinds, especially lobar pneumonia, is usually found with considerably higher frequency among males than among females.

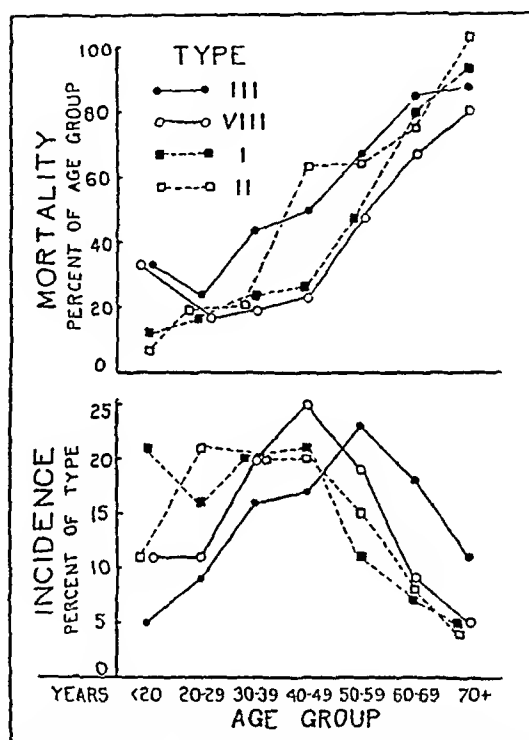


Chart 2.—Comparison between the incidence and mortality, by age groups, of pneumonia of types I, II, III and VIII.

This was found to be true for types III and VIII. There was, however, a wide divergence between the relative percentage of females with pneumonia of types III and VIII and with types I and II. The former groups included 40 and 39 per cent, respectively, of females, whereas only 26 and 14 per cent of the patients with pneumonia of type I and II were females. The distribution of each type of pneumonia between the sexes is shown in chart 3 for all of the cases, for different age groups and for lobar pneumonia and bronchopneumonia. It is seen that the percentage of females increases with age among the patients with type III pneumonia, whereas the highest incidence of females with type VIII pneumonia is among the younger patients. Furthermore,

there are relatively more females than males among the patients with lobar pneumonia of type III and among those with bronchopneumonia of type VIII.

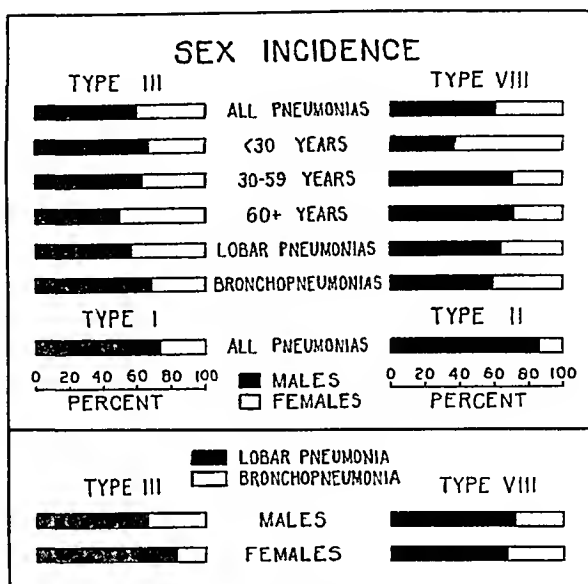


Chart 3.—Sex incidence of type III and type VIII pneumonia and its relation to age and to the character of the pulmonary lesion.

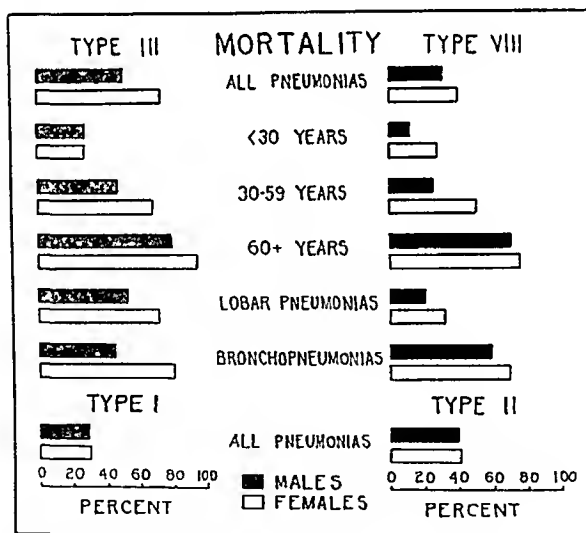


Chart 4.—Mortality from type III and type VIII pneumonia and its relation to sex.

The difference in mortality between the sexes is also of interest (chart 4). There was no significant difference noted among the patients with type I or type II pneumonia. The mortality, however, was higher among the females than among the males both for type III and for type VIII pneumonia. This was true among the patients with type III pneumonia only in the older age groups, in which the incidence was

relatively lower, whereas it was striking in all the patients with type VIII pneumonia except those over 60 years of age, among whom the proportion of females was relatively the lowest.

Thus, as regards sex, type III and type VIII pneumonia have a relatively higher incidence and mortality among females as compared with types I and II. Types III and VIII differ from each other in age distribution and in the incidence of lobar pneumonia and bronchopneumonia. The type III infection has the highest incidence and mortality among elderly females with lobar pneumonia, and the type VIII infection is relatively more frequent and more fatal among the younger female patients and among the females with bronchopneumonia.

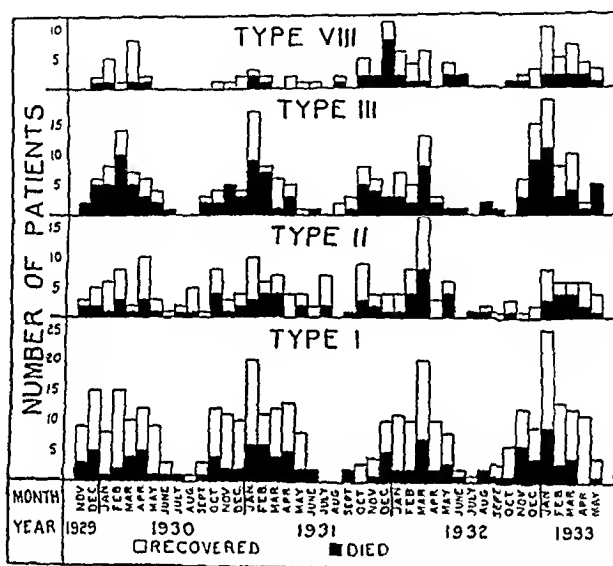


Chart 5.—Monthly incidence of pneumonia of types I, II, III and VIII.

MONTHLY INCIDENCE

The months of highest incidence, as shown in chart 5, were usually the same for pneumonia of types III and VIII as for types I and II. The month in which the largest number of cases occurred differed from year to year. Occasional months showed a high incidence of an individual type of pneumonia without many cases occurring simultaneously among other types.

INCIDENCE OF LOBAR PNEUMONIA AND BRONCHOPNEUMONIA AND RELATION TO MORTALITY

Earlier in this paper attention was called to the uniformity with which types I and II pneumococci are associated with lobar pneumonia. It was also pointed out that, of the three commonest types of pneumococci, type III alone is associated with bronchopneumonia and with conditions other than pneumonia in a large number of cases (table 3).

These facts correlate with the more frequent finding of this type in the mouths of normal persons and also with the higher percentage of mixed infections with this type, as compared with all other types, particularly I and II. The patients from whom type VIII pneumococci were isolated also showed a high percentage of conditions other than pneumonia and an even greater relative incidence of bronchopneumonia than was found among those from whom type III was obtained. It is of interest to compare the two types further with respect to their association with lobar pneumonia and bronchopneumonia and to observe the age distribution and mortality of these clinically different conditions.

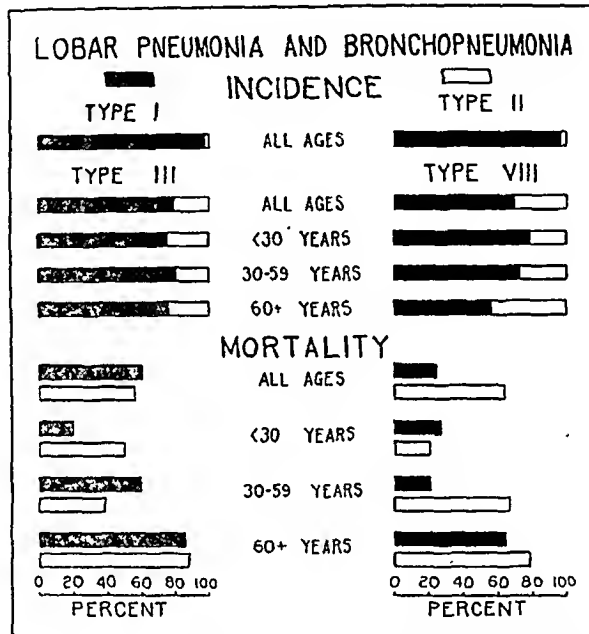


Chart 6.—Incidence and mortality of type III and type VIII lobar pneumonia and bronchopneumonia in different age groups.

In chart 6 it will be seen that while 21 and 30 per cent, respectively, of the type III and type VIII infections were considered "atypical" pneumonia or bronchopneumonia, only a small percentage of the cases of pneumonia of types I and II were diagnosed as bronchopneumonia (3 and 5 per cent, respectively). The incidence of bronchopneumonia was the same in each age group among the patients with type III pneumonia but increased with age among those with type VIII. With respect to mortality also, type III and type VIII pneumonia differed. For all of the type III infections the mortality was the same in patients with lobar pneumonia as in those with bronchopneumonia, although the young and the middle age group varied. The mortality was distinctly higher, however, in the patients with type VIII bronchopneumonia, especially in the middle age group and in the patients 60 or older. The

difference in incidence and mortality among males as compared with females has already been referred to (charts 3 and 4).

Thus the type III and type VIII infections are similar in that a relatively large portion are bronchopneumonia. They differ in that type VIII bronchopneumonia is relatively more frequent in older patients and in females (chart 3). In type III pneumonia the mortality is the same with both types of lesion, whereas bronchopneumonia due to the type VIII pneumococcus is more fatal than lobar pneumonia of the same type, especially in the middle age group.

TABLE 4.—Primary Conditions in Patients with Secondary Pneumonia*

	Age, Years	Opera- tion		Cardiac Failure		Bronchial Asthma (Acute)		Sepsis and Acute Infec- tions		Cancer (Term- inal)		Frac- tures		Miscel- laneous Condi- tions†		Total‡	
		R§	D§	R	D	R	D	R	D	R	D	R	D	R	D	R	D
Type III pneu- monia	29 and under	3	..	1	2	2	1	5	3
	30 to 49	3	2	2	1	1	3	1	1 ¹	7	7
	50 to 69	6	2	1	9	1	1	..	2	..	5	..	1	..	2 ²	8	22
	70 and over	1	8	1	8
	All.....	12	4	3	17	3	2	3	7	0	5	1	2	0	3	22	40
Type VIII pneu- monia	29 and under	2	..	1	1	1	..	1 ³	3	3
	30 to 59	1	2	1	1	..	1	..	2	..	1	..	1	..	2 ⁴	2	10
	60 and over	4	2 ⁵	0	6
	All.....	3	2	2	5	0	1	0	3	0	1	0	2	0	5	5	19

* Excluding acute infections of the upper respiratory tract (common cold, grip, influenza, acute bronchitis), alcoholism and chronic disease not directly related to the onset of pneumonia.

† The superior figures indicate the following conditions: (1) diabetic gangrene; (2) pernicious anemia (1 case) and cerebral hemorrhage (1 case); (3) dermatitis exfoliativa; (4) hemolytic jaundice (1 case) and pemphigus (1 case); (5) cerebral hemorrhage (1 case) and cirrhosis of the liver and hematemesis (1 case).

‡ Of the cases of type III pneumonia, 30 were lobar pneumonia; of these 18 patients died. Of the cases of type VIII pneumonia, 5 were lobar pneumonia; of these patients 4 died.

§ R indicates recovered; D, died.

SECONDARY PNEUMONIA

Under the term "secondary pneumonia" are classed all cases in which pneumonia developed during a severe acute illness or during an acute episode in the course of a chronic illness. We have excluded, for convenience, all cases of alcoholism, acute or chronic, and all cases in which the pneumonia began during or shortly after a common infection of the respiratory tract, such as common cold, grip, influenza or acute bronchitis. Cases of cardiac disease are included only if there was definite decompensation before the onset of the pneumonia. Postoperative pneumonia is included.

The various diseases during the course of which secondary pneumonia occurred are shown in table 4. The commonest was cardiac failure in old people, in whom this condition and the superimposed pneumonia were usually fatal.

The incidence and mortality of secondary pneumonia, as compared with the remaining cases, which for convenience are termed "primary," are shown in table 5. It is seen that the majority of the cases of bronchopneumonia and only a small percentage of those of lobar pneumonia are secondary. The mortality from secondary pneumonia is apparently the same whether the resulting pulmonary lesion is lobar pneumonia or bronchopneumonia. Among the patients with type III infections, the mortality is the same for all lobar pneumonia, primary and secondary, whereas secondary bronchopneumonia causes more than twice the mortality of primary bronchopneumonia. Type VIII secondary pneumonia causes approximately four times as high a fatality as the primary cases regardless of the anatomic distribution of the pulmonary lesion.

TABLE 5.—Incidence and Mortality of Secondary Pneumonia

		Secondary Pneumonia					Primary Pneumonia			
		Total Num- ber of Cases	Num- ber of Cases	Num- ber of Deaths	Mor- tality, per Cent	Inci- dence, per Cent of Type	Num- ber of Cases	Num- ber of Deaths	Mor- tality, per Cent	Inci- dence, per Cent of Type
Type III pneu- monia	Lobar pneumonia	177	30	18	60	17	147	90	61	83
	Bronchopneumonia	48	32	22	69	67	16	5	31	33
	All.....	225	62	40	64	28	163	95	58	72
Type VIII pneu- monia	Lobar pneumonia	73	5	4	80	7	68	14	21	93
	Bronchopneumonia	32	19	15	79	59	13	5	38	41
	All.....	105	24	19	79	23	81	19	23	77

PREDISPOSING FACTORS

We shall consider only two groups of predisposing factors, somewhat arbitrarily subdivided. These probably constitute most of the important conditions affecting the occurrence and outcome of pneumococcic pneumonia. Such factors as exposure to cold, to wet or to other unfavorable conditions have not been considered, since they were not frequently encountered.

Alcoholism and Chronic Diseases.—The incidence of these conditions is shown in table 6. Alcoholism and degenerative cardiovascular disease (the cases in which cardiac failure preceded the onset of pneumonia are excluded here) were the most frequent, especially in the fatal cases. Among the patients with acute alcoholism are included only those who were acutely intoxicated at the time of admission or in whom delirium tremens developed during the course of the disease. The mortality among the patients with acute alcoholism was very high, both for type III and for type VIII pneumonia. In all but a small percentage of the entire group there was typical lobar pneumonia. The mortality among these patients was similar to that for all of the patients with pneumonia of the same type.

Antecedent Respiratory Infections.—Acute infections of the respiratory tract, including the common cold, influenza, grip and acute bronchitis, preceded the onset of the pneumonia in about one half of all of the patients for whom a history was obtained, as shown in table 7.

TABLE 6.—Incidence of Alcoholism and Chronic Diseases Not Directly Related to the Onset of Pneumonia

Age, Years	Alcoholism				Arterio- sclerosis and Hyper- tension	Chronic Respira- tory Disease	Chronic Nonre- spiratory Infec- tions	Rheu- matic Heart Disease	Cirrhosis of Liver	Other Condi- tions	Total							
	Chronic		Acute								R	D	R	D	R	D	R	D
	R*	D*	R	D														
Type III Pneumonia																		
29 and under	1	1	1	1	..	2	2	1	..	1	1	6	5			
30 to 49	4	4†	1	7†	1	..	1	2	5	1	1	1	3	14	17			
50 to 69	3†	5	3‡	8	3	11	2	5	1	3	1	5	12	37		
70 and over	1	6	1	2	..	1	1	1	3	11		
All.....	9	10	5	16	4	17	6	11	7	5	2	3	1	3	35	70		
Type VIII Pneumonia																		
29 and under	5	..	1	1	1	1		
30 to 59	9§	2	3	3¶	1	4	4	1	1	2	14	10	
60 and over	..	1	1	..	1	2	1		
All.....	9	3	3	3	2	4	10	1	1	1	0	0	0	0	23	13		

* R indicates recovered; D, died.

† Including 1 with cirrhosis of the liver.

‡ Including 1 with diabetes.

§ Including 1 with secondary anemia and 1 with chronic bronchitis.

|| Including 2 with chronic respiratory disease.

¶ Including 1 with hypertension and 1 with chronic bronchitis.

TABLE 7.—Incidence and Mortality of Cases of Pneumonia in Which a History Regarding Antecedent Respiratory Infections Was Obtained

	Total Number of Cases	Cases with Antecedent Respiratory Infections				Cases Without Antecedent Respiratory Infections			
		Num- ber of Cases	Inc- idence, per Cent	Num- ber of Deaths	Mor- tality, per Cent	Num- ber of Cases	Inc- idence, per Cent	Num- ber of Deaths	Mor- tality, per Cent
Type III pneumonia									
Lobar pneumonia.....	157	78	50	45	59	79	50	44	56
Bronchopneumonia.....	37	14	38	4	28	23	62	14	61
All cases.....	194	92	47	49	53	102	53	58	57
Type VIII pneumonia									
Lobar pneumonia.....	66	38	58	7	18	28	42	8	28
Bronchopneumonia.....	29	14	48	6	43	15	52	11	73
All cases.....	95	52	55	13	25	43	45	19	44

They were somewhat more common among the patients with type VIII pneumonia (55 per cent of those for whom a history could be obtained) than among those with type III (47 per cent). They were slightly more frequent in lobar pneumonia than in bronchopneumonia of either type. Although this is not shown in the table, they were found to be slightly more common in the younger patients with each type of pneu-

monia. Among the patients with bronchopneumonia the mortality was much higher when there was no history of an antecedent respiratory infection than when such an infection had occurred. This is probably accounted for by the fact that many of the cases of bronchopneumonia without respiratory infections were secondary.

CLINICAL FINDINGS

It was pointed out by Blake¹⁵ that the symptoms and course of pneumonia caused by the type III pneumococcus are similar to those of pneumonia caused by other types. This we have found, in general, to be true for both type III and type VIII pneumonia. Furthermore,

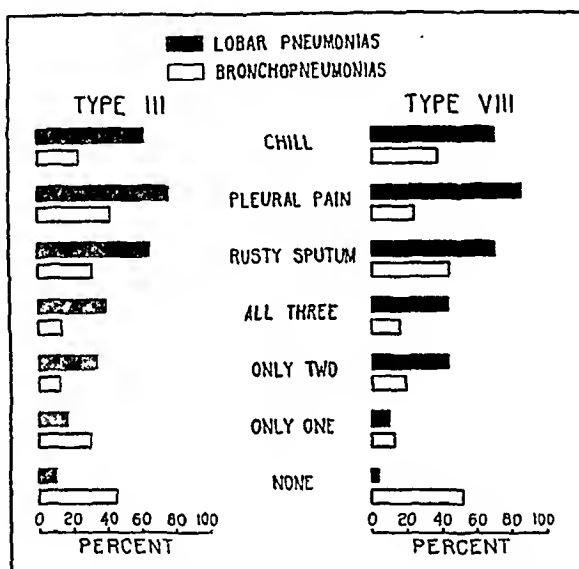


Chart 7.—Incidence of three cardinal symptoms of pneumonia in type III and type VIII lobar pneumonia and bronchopneumonia.

the symptomatology appears to be more closely related to the anatomic lesion than to the etiologic type.

Mode of Onset.—The onset was sudden in the majority of cases of lobar pneumonia and gradual in most of the cases of bronchopneumonia of both types. A sudden onset occurred in 72 per cent of the cases of lobar pneumonia of type III and in 81 per cent of those of type VIII, but only in 40 and 33 per cent, respectively, of the cases of type III and type VIII bronchopneumonia. The two most common initial symptoms in lobar pneumonia were chill and pain in the chest, one or both of these ushering in the disease in 69 per cent of the cases of type III lobar pneumonia and in 74 per cent of those of type VIII. No single symptom characterized the onset of bronchopneumonia, the most common initial symptom being fever, cough or dyspnea, each of which occurred at the onset in less than one fourth of the cases.

Cardinal Symptoms.—The cardinal features of lobar pneumonia characterized the picture of this disease, as contrasted with that of bronchopneumonia, in both the type III and type VIII cases. In chart 7 is indicated diagrammatically the frequency with which three of the cardinal symptoms, namely, chills, pain in the chest and rusty or blood-tinged sputum, were present separately or in combination in the cases of lobar pneumonia and bronchopneumonia of each type. Two or all three of these symptoms were present in 73 per cent of the cases of type III lobar pneumonia and in 85 per cent of those of type VIII,

TABLE 8.—*Extent of Pulmonary Lesion*

Age, Yrs.	Lobar Pneumonia											Broncho- pneumonia				
	Right Lung						Left Lung			Bilateral		Most- ly Right	Most- ly Left	Bilat- eral		
	Middle Upper and and			Entire	Lower	Upper	Entire	2 Lobes	3 or More Lobes							
	Lower	Middle	Upper													
	R*D*	R D	R D	R D	R D	R D	R D	R D	R D	R D	R D	R D	R D	R D		
Type III Pneumonia																
19 and under	5	2	1	1	3
20-29	1	1	1	1	2	1	2	5	1	1	..	1	..	2
30-39	5	3	..	1	2	1	2	5	1	..	1	1	2	1	..	2
40-49	3	5	..	6	3	1	..	3	1	1	..	3	1	1	2	2
50-59	4	3	..	5	..	2	3	3	5	1	1	5	2	3	1	3
60-69	0	2	1	1	..	2	1	2	2	1	3	..	2	..	3	1
70 and over	1	3	..	2	1	2	1	1	..	5	1	..	2	4
All	19	17	2	1	8	14	4	5	1	8	6	12	21	11	3	20
Type VIII Pneumonia																
19 and under	1	1	1	2	..	1	..	2	1	..	1	1
20-29	2	2	2	1	1	1	..	1	..	1
30-39	8	1	3	..	1	..	1	..	1	1	2
40-49	6	3	..	5	1	..	1	4	1	1	1	1
50 and over	1	2	..	1	2	3	3	1	1	2	4	10
All	18	6	0	0	9	1	0	6	4	1	1	3	2	3	5	14

* R indicates recovered; D, died.

as contrasted with only 25 and 35 per cent, respectively, of the cases of bronchopneumonia of these types.

Extent of Consolidation.—The frequency with which various lobes were involved in persons of different age groups is shown in table 8. In general, the lesion tended to be localized in one lobe or in one lung in the young patients with type III lobar pneumonia. Otherwise, no relation was observed between the patient's age and the location of the lesion. There was a direct relationship between the extent of involvement and the mortality. The right lung was involved about twice as frequently as the left. Among the patients with type III lobar pneumonia, involvement of the upper lobe was associated with a higher mortality, but this was not true among the patients with type VIII lobar pneumonia. Among the patients with bronchopneumonia, the lesion was

bilateral in two thirds of the cases of each type. When, however, the lesion was largely limited to one side, it was more commonly on the right.

Duration of Disease and Mode of Termination.—We have arbitrarily defined as crisis a permanent drop in temperature to 100 F. and obvious coincident clinical improvement occurring within twenty-four hours. If this change occurred over a longer period, the day that the temperature first dropped to 101 F. was considered as the day when lysis took place. By these criteria, only 33 per cent of the patients with type III lobar pneumonia and 27 per cent of those with type VIII who recovered and even fewer of the patients with bronchopneumonia showed recovery by crisis. Almost all of the patients who recovered by crisis were under 50 years of age.

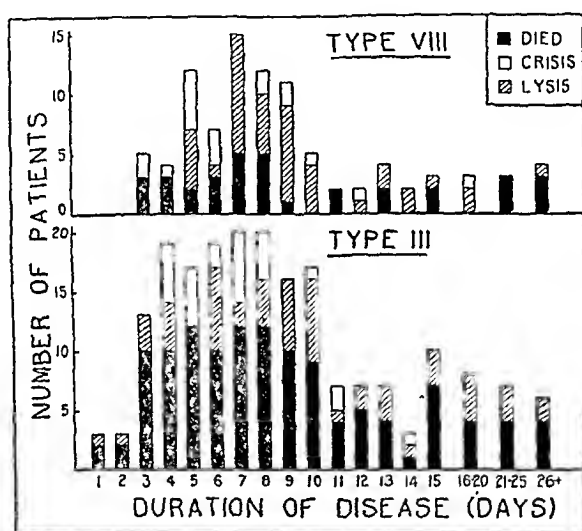


Chart 8.—Duration and outcome in type III and type VIII pneumonia.

The duration of the disease and the mode of recovery in all of the cases of pneumonia are shown graphically in chart 8. Seventy-three per cent of the cases of type III pneumonia in which the duration of the disease could be determined terminated before the end of the tenth day, and 70 per cent of those of type VIII pneumonia terminated before the end of the ninth day. Termination by crisis in type III pneumonia usually occurred before the eighth day. About 10 per cent of the cases of each of these two types of pneumonia lasted longer than fifteen days.

Relation of Leukocyte Count to Outcome.—The high mortality among patients with pneumonia associated with leukopenia has frequently been noted. It was thought to be of interest to compare the leukocyte level in type III and type VIII pneumococcic pneumonia in different age groups. The frequency with which different levels of the blood leukocytes were observed is shown in table 9. In spite of the

striking difference in mortality between these two types of pneumonia, the frequency with which different white blood cell levels were encountered was strikingly similar. Leukopenia was infrequent in both of these types. All but 1 of the patients with less than 5,000 white corpuscles per cubic millimeter of blood died; otherwise no striking relationship existed between the level of the leukocytes and the outcome. Leukocyte counts over 30,000 were infrequent. The mortality in such cases was slightly higher than the average. Only slight differences were observed among the different age groups, leukopenia being relatively uncommon in the young patients and high leukocyte counts slightly less common in the very old patients.

TABLE 9.—*Leukocytosis and Mortality in Different Age Groups*

		Leukoeytes per Cubic Millimeter									
		Less Than 5,000		5,000 to 10,000		10,000 to 20,000		20,000 to 30,000		30,000 and Over	
		R*	D*	R	D	R	D	R	D	R	D
Type III pneu- monia	Age, Years										
	29 and under.....	0	1	1	2	11	3	5	0	3	1
	30 to 49.....	0	2	3	4	20	17	6	3	1	1
	50 to 69.....	0	2	5	4	8	24	3	12	1	4
	70 and over.....	0	1	0	4	2	10	0	2	0	2
	All.....	0	6	9	14	41	54	14	17	5	8
Type VIII pneu- monia	Mortality, per cent	100		61		57		55		63	
	Incidence, per cent	4		14		57		18		8	
	29 and under.....	0	0	3	1	7	1	6	3	1	1
	30 to 49.....	1	4	5	1	19	5	10	1	4	0
	50 and over.....	0	1	4	3	6	9	1	1	0	2
	All.....	1	5	12	5	32	15	17	5	5	3
	Mortality, per cent	83		29		32		23		37	
	Incidence, per cent	6		17		47		22		8	

* R indicates recovered; D, died.

Complications.—Purulent complications were observed during life in about 10 per cent of the cases of each type. In the type III cases, most of these complications were in association with lobar pneumonia, whereas one half of those observed in the type VIII cases were associated with bronchopneumonia. The number of the various complications observed is shown in table 10.

BACTEREMIA

Blood cultures were made on one or more occasions during life in 131 patients with type III and in 68 patients with type VIII pneumococcic pneumonia. Positive cultures were obtained in 46 of the former, an incidence of 35 per cent, and in 21 of the latter, an incidence of 31 per cent. No instance of recovery was observed in any patient with type III pneumococcic bacteremia,^{22a} whereas only 43 per cent of the

22a. Since this paper was submitted we have observed 2 patients, aged 46 and 62, respectively, who had lobar pneumonia and type III pneumococcus bacteremia and recovered without complications.

patients with type VIII bacteremia died. The mortality in patients with sterile blood cultures was 34 per cent and 21 per cent among the patients with type III and type VIII pneumonia, respectively.

Pour plates and colony counts were made for over one half of the patients. Among 7 patients with type VIII pneumococcic bacteremia for whom pour plates were made, 4 showed less than 10 colonies per cubic centimeter of blood, and the remaining 3 showed 11, 24 and 2,000 colonies, respectively. Among 26 patients with type III bacteremia in whom the extent of invasion of the blood was quantitated, 6 showed no colonies on plates (that is, only the broth culture was positive), 9 showed less than 20 colonies per cubic centimeter and the remaining

TABLE 10.—Incidence of Complications* (Diagnosed During Life)

	Type III Pneumonia		Type VIII Pneumonia	
	Recovered	Died	Recovered	Died
Empyema	3	9	6	2
Pulmonary abscess and empyema.....	..	2	..	1
Pericarditis	2
Meningitis	2†	..	2
Otitis media	1	1
Sterile pleural effusions.....	1	6	3	1
Miscarriage	1	..	1
Jaundice	6	17‡	4	2
Atelectasis	2	..	2	1
Conjunctivitis	1	..
Hemoptysis	1
Pulmonary infarcts§	1	1
Pneumothorax and jaundice.....	1

* Not including mixed infections with other organisms.

† One patient had otitis media also.

‡ One patient had pneumothorax also.

§ Patients with rheumatic heart disease.

11 showed 75 or more colonies. In 5 of the latter, more than 1,000 colonies per cubic centimeter were observed in the later cultures.

The relation of bacteremia to age, to the outcome and to the stage of the disease is shown for type III pneumonia in chart 9 and for type VIII in chart 10. In type III pneumonia, death in young patients was usually associated with bacteremia, and the incidence of bacteremia among patients who died diminished with advancing age. The incidence of bacteremia increased during the course of the fatal cases, but showed a decline after the fifteenth day of the disease. In type VIII pneumonia, bacteremia occurred with increasing frequency among patients with fatal cases in advancing age groups, whereas, among the patients who recovered it was frequent only in the middle age group. Conversely, the mortality was relatively higher in patients with bacteremia in the older age group. In the fatal cases the highest incidence of bacteremia occurred before the ninth day, after which the blood culture was usually negative.

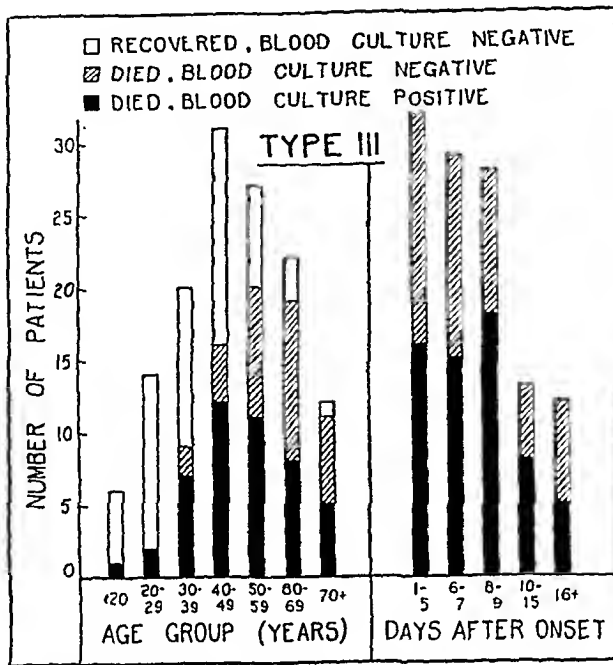


Chart 9.—Bacteremia in type III pneumonia in relation to the age of the patients and the outcome (left) and in relation to the duration of the disease in fatal cases (right).

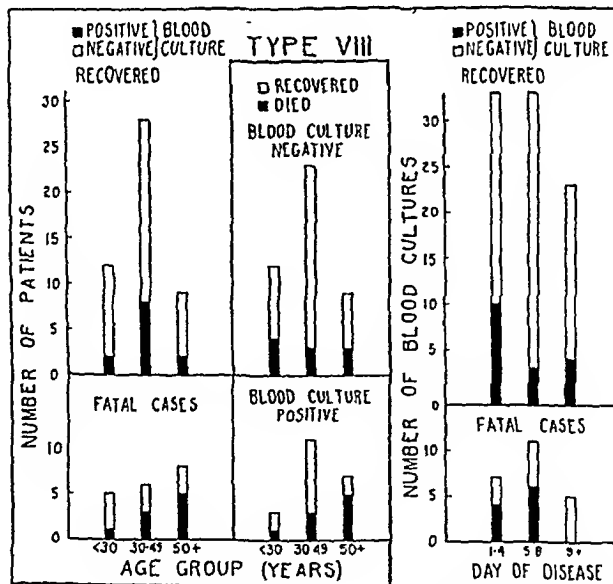


Chart 10.—Bacteremia in type VIII pneumonia in relation to the age of the patients and the outcome (left) in relation to the mortality among patients with positive blood cultures and among those with negative blood cultures (center) and in relation to the duration of the disease in patients who recovered and in those who died (right).

In table 11 are shown the results of blood cultures in a group of 14 cases of type III pneumonia in which both positive and negative cultures were obtained. The number of cases is small, but they indicate that bacteremia may develop late and may be transient and that death may ensue in spite of the fact that bacteremia has subsided.

Invasion of the blood by other organisms was observed in 5 patients with type III pneumonia. One of these had type XI pneumococci in the blood on two occasions and subsequently recovered. Another patient who died had type I pneumococci in the blood twice and both type I and type III pneumococci in the sputum. A third patient showed type I

TABLE 11.—*Relation of Bacteremia to the Course of the Disease in Patients with Type III Pneumonia in Whom Both Positive and Negative Blood Cultures Were Obtained*

Case	Age, Yrs.	Results of Blood Cultures* Day of Disease															Autopsy, Hours Post Mortem	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		16
1	62	+	0	D	0
2	57	+	+0	D	..	+	..	0	..	0D
3	44	0	+	+	D
4	64	0	0	0	..	0	D+	..	4
5	45	0	..	+	..	+	D
6†	55	+	+	++	+D0	2
7	71	+	+	..	D
8	54	0	..	0	D
9‡	63	0D	+	16
10	39	0	..	+	..	D+	6
11‡	60	0	..	+	D	0	12
12	21	0	+	..	D
13	49	0	0	+	D
14§	43	III	+D

* 0 indicates negative blood culture; +, blood culture positive for *Pneumococcus* type III; D, died; I, blood culture positive for *Pneumococcus* type I.

† Treated with homologous convalescent serum.

‡ Bronchopneumonia.

§ Treated with Felton's serum (type I and II antibody solution). This patient had type I and type III pneumococci in the sputum.

pneumococci and probably no type III organisms in the blood on three occasions within the same day, and the fourth examination showed only type III pneumococci (case 14, table 11). This patient was treated with Felton's serum. Both type I and type III pneumococci were recovered from the sputum and from the fluid obtained by puncture of the lung post mortem. Two other patients with type III pneumococci in the sputum showed hemolytic streptococci in the blood, one before death and the other in the heart's blood post mortem.

One of the patients with type VIII pneumonia had hemolytic streptococci, and another had Friedländer bacilli, in the heart's blood at autopsy. Both of these patients showed type VIII pneumococci in the lungs. A third patient had type VIII pneumococci in the sputum, but only hemolytic streptococci were recovered from the heart's blood and lungs at autopsy.

POSTMORTEM OBSERVATIONS

The gross and microscopic observations in the cases that came to autopsy were reviewed, and a summary of the important findings is presented in table 12. The high incidence of bronchial involvement in type III lobar pneumonia is of interest. In most instances the mucosa of the trachea, bronchi and bronchioles was thickened and inflamed and contained an inflammatory exudate which, for the most part, was thick and mucopurulent. In many instances, however, a frank purulent exudate was observed. Empyema was noted in the type III cases only in association with lobar pneumonia. The amount of purulent exudate in the pleural cavity varied, being less than 100 cc. in 4 cases and over

TABLE 12.—*Summary of Postmortem Observations Relating to Lungs and Adjoining Structures*

	Type III		Type VIII	
	Lobar Pneumonia	Broncho- pneumonia	Lobar Pneumonia	Broncho- pneumonia
Number of cases	46*	18	8	13
Tracheitis and bronchitis.....	27	12	2	5
Serofibrinous effusion	7†	4‡	2	1
Empyema	11	0	2	1
Abscesses of lung.....	15‡	1§	1	1
Pericarditis	3	0	0	0
Meningitis	0	1	1	1
Vegetative endocarditis	1	0	0	0
Pulmonary involvement:				
Limited to one lobe.....	13	0	3	0
Unilateral, in more than one lobe.....	18	5	1	2
Bilateral	15	13	4	11
Shiny mucoid cut surface.....	10	1	0	0

* Includes one patient that had patchy involvement of one lung and lobar consolidation in the other.

† Two were bilateral.

‡ Three were observed only microscopically.

§ Diagnosed microscopically.

500 cc. in 4; the exudate was unilateral in every instance. The sero-fibrinous effusions also varied in amount. In 1 case of type III lobar pneumonia there was 500 cc. in one pleural cavity and 1,400 cc. in the other; in the remaining cases there was 200 cc. or less. In all of the cases of type III bronchopneumonia, the pleural cavity contained 250 cc. or more. The most significant finding, however, was the high incidence of parenchymatous destruction and abscess formation in the type III lobar pneumonia. This was found in one third of these cases, an incidence much higher than has been observed in any other group. A shiny, mucoid appearance of the cut surface, thought to be characteristic of type III as contrasted with other types of lobar pneumonia, was not so frequent as was expected, although the type III pneumococcus was obtained directly from the lungs in all but 5 of the cases.

Most of the findings in the cases of type III pneumonia are consistent with the longer duration of the disease which has been noted. In the early description of Richardson,⁹ these findings, coupled with

the scarcity of organisms and the failure to find the usual characteristic pneumococci, were interpreted as indicating that the type III organisms, which he found and described under the names "*Streptococcus mucosus*" and "pseudopneumococci," were probably late secondary invaders.

COMMENT

This description of two different diseases, caused by related organisms that can be differentiated only by bacteriologic methods, is of practical importance as well as of theoretical interest. The facts presented are useful in diagnosis and in prognosis and are of potential value in epidemiology and in therapy.

In regard to prognosis, the data indicate clearly the striking differences in the death rate associated with pneumonia due to these two organisms.

As to diagnosis, it is probable that a certain number of cases caused by type VIII pneumococci have been classified among those of type III pneumonia because of the rather marked cross-agglutination that may occur with some of the more reactive strains of these types. One would expect that the separation of such cases of type VIII pneumonia, having a lower death rate, from the cases of type III pneumonia would leave a group that would collectively appear more severe than the disease previously associated with the type III pneumococcus.

That this may have occurred is shown by the information available with regard to bacteremia. While most observers have found the death rate in cases of pneumonia with type III pneumococcic bacteremia to be high, they have noted recoveries with varying frequency.²³ Among the cases reported here, 100 per cent of those with type III bacteremia ended fatally. It seems possible that some of the patients with pneumonia reported by others to have recovered following type III pneumococcic bacteremia really had type VIII infections.

Some strains of type VIII pneumococci were probably also included among the organisms used in some attempts to produce potent type III antiserums, although these strains were sometimes recognized as atypical.¹² Such errors did not account for the major difficulties encountered in this work, as most of the organisms used gave the reactions characteristic of the typical strains of type III pneumococci.

The more careful recognition of the etiologic agents in cases of bronchial and atypical pneumonia may help in elucidating some of the factors responsible for the occurrence of these rather poorly understood diseases. It is well known that such cases are common and that they are given less attention than their frequency and importance deserve.

23. Warr, O. S., and Alperin, J.: Lobar Pneumonia: A Report of 2,039 Cases, *Ann. Int. Med.* 6:1474 (May) 1933.

It is especially important to understand the reasons for the occurrence of bronchial and secondary pneumonia in hospitalized patients and in others, since the whole course is frequently observed by the physician. Such an understanding depends, in large part, on a knowledge of the strains of bacteria, usually pneumococci, that are involved and on the determination of their source. This epidemiologic aspect of secondary and bronchial pneumonia will be furthered by the accurate determination of types of pneumococci.

The differentiation of serologically specific strains of related organisms also has potential value in regard to therapy. Thus far, the significant successes in combating pneumococcic infections have been obtained with strictly type-specific agents. This has been true with respect to the vaccines used in prophylaxis²⁴ and the serum used in the treatment of lobar pneumonia and with respect to the enzymes used in curing animals of experimental infections with type III pneumococci.²⁵ In order to use any of these methods of approach, one must first recognize the specific nature of the causative agent of the disease.

SUMMARY

A review is presented of the major findings in a consecutive series of 282 patients from whom the type III pneumococcus was obtained and 125 patients from whom the serologically related type VIII pneumococcus was obtained at the Boston City Hospital between November, 1929, and May, 1933. In particular, 225 cases of type III pneumococcic pneumonia were compared with 105 cases of type VIII pneumococcic pneumonia.

A large proportion of type III and type VIII pneumococci were recovered from patients who did not have pneumonia. Type I and type II pneumococci were comparatively rare in patients without pneumonia.

24. Lister, F. S.: An Experimental Study of Prophylactic Inoculation Against Pneumococcal Infections in the Rabbit and in Man, Publications of the South African Institute for Medical Research, no. 8, 1916. Lister, F. S.: Prophylactic Inoculation of Man Against Pneumococcal Infections, and More Particularly Against Lobar Pneumonia, Publications of the South African Institute for Medical Research, no. 10, 1917. Cecil, R. L., and Austin, J. H.: Results of Prophylactic Inoculation Against Pneumococcus in 12,519 Men, *J. Exper. Med.* **28**:19 (July) 1918. Cecil, R. L., and Vaughan, H. F.: Results of Prophylactic Vaccination Against Pneumonia in Camp Wheeler, *ibid.* **29**:457 (May) 1919.

25. Avery, O. T., and Dubos, R.: The Protective Action of a Specific Enzyme Against Type III Pneumococcus Infection in Mice, *J. Exper. Med.* **54**:73 (July) 1931. Goodner, K.; Dubos, R., and Avery, O. T.: The Action of a Specific Enzyme upon the Dermal Infection of Rabbits with Type III Pneumococcus, *ibid.* **55**:393 (March) 1932.

About one fifth of the pulmonary infections with the type III pneumococcus and one third of those with type VIII were bronchopneumonia, whereas only 3 per cent of the infections due to the type I pneumococcus and 5 per cent of those due to type II were bronchopneumonia.

Mixed infections with other significant organisms were more frequent in type III and type VIII pneumococcic pneumonia (especially the former) than in any other type.

The proportion of females among the patients with type III and type VIII pneumonia was two or three times as great as among the patients with pneumonia of types I and II. Furthermore, the mortality in the latter types was the same for both sexes, whereas it was appreciably higher among females with both type III and type VIII pneumonia.

Bronchopneumonia was more frequent among the patients with type VIII than among those with type III pneumonia. The mortality among those with type III infections was the same for bronchopneumonia as for lobar pneumonia. Type VIII bronchopneumonia caused a mortality more than twice as high as that of lobar pneumonia of the same type.

The majority of cases of bronchopneumonia of both types were secondary and began during the course of some other serious illness or following an operation. Only a small percentage of the cases of lobar pneumonia were secondary. The mortality in secondary pneumonia was from two to four times as high as in primary pneumonia, except in secondary lobar pneumonia due to the type III pneumococcus. In the latter cases, the mortality was the same as in primary pneumonia of the same type.

Alcoholism and chronic disease were common predisposing factors in both type III and type VIII pneumonia. Chronic infections of the respiratory tract and degenerative cardiovascular disease were the most frequent. Acute infections of the respiratory tract preceded the onset in one half of the cases of both types. Except in type III lobar pneumonia, the mortality was lower in patients who had an antecedent respiratory infection than in those who did not.

The clinical features in type III and type VIII pneumonia were similar to those found in types I and II. Sudden onset, chill, pleural pain and rusty sputum were the predominant features among the patients with lobar pneumonia of both types and were relatively uncommon among the patients with bronchopneumonia.

Leukopenia was rare in both types of pneumonia. It was significant only when the level of the leukocytes dropped below 5,000 per cubic millimeter of blood.

The duration of the disease was somewhat longer in type III than in type VIII pneumonia. Recovery by crisis was relatively uncommon in both types. It occurred more frequently in young persons who recovered early.

Bacteremia was present in about one third of the cases of both types. All of the patients with pneumonia and type III pneumococcic bacteremia died; 43 per cent of those with type VIII pneumococcic bacteremia died. The degree of the invasion of the blood was greater in type III pneumonia.

The most significant postmortem observation was the finding of areas of necrosis in the consolidated areas in one third of the cases of type III lobar pneumonia.

These two types of pneumococci produce diseases which differ, in similar ways, from pneumonia caused by types I and II but which exhibit striking differences from each other. The importance of differentiating these organisms has been discussed.

ACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS

REPORT OF FOUR CASES, WITH AUTOPSY OBSERVATIONS
IN TWO

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AND

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The fact that *Streptococcus viridans*, usually a nonpathogenic organism regularly residing as a saprophyte in the teeth, tonsils, vagina and other organs, can be the cause of fatally terminating endocarditis was discovered by Schottmueller.¹ This author was the first to demonstrate that in order to cause endocarditis this organism must implant itself on a previously diseased or congenitally deformed valve, the order of frequency in case of a diseased valve being a rheumatic valve, more rarely a syphilitic valve and still more rarely an arteriosclerotic valve. When Schottmueller recognized that this form of endocarditis, which he still believes can be caused only by *Str. viridans*, almost always has a protracted course, he named it "endocarditis lenta."

Libman² and his associates, notably Celler,³ working in this country, have found, however, that similar pathologic changes in a chronically diseased valve, giving rise to a like clinical course, can be caused by organisms other than *Str. viridans*, principally by pneumococci, the influenza bacillus, gonococci, staphylococci, hemolytic streptococci and members of the genus *Proteus*. Therefore, Libman named the disease "subacute bacterial endocarditis." As his work has been confirmed by many authors, both in the United States and abroad, this name has continued in use.

Although subacute bacterial endocarditis is frequently encountered, acute *Str. viridans* endocarditis occurs so seldom that even such observers as Schottmueller, Bingold,⁴ Blumer,⁵ Thayer⁶ and others have

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2. Libman, E.: Endocardial Lesions of Subacute Bacterial Endocarditis, Am. J. M. Sc. **144**:313, 1912.

3. Libman, E., and Celler, H. L.: Etiology of Subacute Infective Endocarditis, Am. J. M. Sc. **140**:516 (Oct.) 1910.

4. Bingold, K.: Septische Erkrankungen, Neue deutsche Klin. **9**:689, 1932.

5. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105 (May) 1923.

6. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926.

reported very few cases. Because of this rarity, we believe that a description of four cases that have recently come under our observation will be of interest.

Whatever organism causes subacute endocarditis, the existing pathologic process in the valve to a large extent determines the clinical picture. That is, the excrescences on the valve serve as a focus of infection, giving rise to protracted illness. In the acute cases, on the other hand, although the valve shows evidences of polypi and ulceration—sometimes more ulceration than polypous excrescences—the picture is primarily that of true septicemia.

The salient symptoms and signs of typical subacute bacterial endocarditis are well known; those of acute *Str. viridans* endocarditis are less familiar. We believe that the picture of the latter condition will best emerge if, in addition to stating the findings in our cases, we preface these by a somewhat detailed outline of the features of subacute bacterial endocarditis, which will make the differences between the two conditions more readily apparent.

SUBACUTE BACTERIAL ENDOCARDITIS

An outstanding feature of subacute bacterial endocarditis, and one that immediately distinguishes it from acute *Str. viridans* endocarditis, is that the temperature curve is not characteristic; in fact, the more protracted the course of the disease, the less tendency there is to a septic type of temperature. The temperature may be transiently very high, with the patient extremely euphoric, as in typhoid, but it is far more often subfebrile. The blood pressure is not elevated as a rule. The pulse is seldom rapid until the terminal stage of the disease, when multiple emboli begin to occur. In nearly all cases there is secondary anemia—the café au lait anemia described by Libman. Tenderness over the sternum is generally present on percussion. Clubbing of the fingers, particularly red clubbing, is an important symptom. Janeway's nodes on the tips of the phalanges or on the tips of the toes, extremely tender to touch, are diagnostic. White-centered petechiae in the conjunctivae are also diagnostic.

The patient is seldom heart-conscious, all cardiac symptoms being in the background. There is rarely any cardiac decompensation, because persons in whom there is decompensation rarely have subacute bacterial endocarditis. As a rule, there is neither fibrillation nor any other form of arrhythmia. A murmur is always present but is changeable in character; because of the associated anemia it is sometimes wrongly interpreted as a hemic murmur. As this form of endocarditis implants itself most often on a previously diseased aortic valve (aortic insufficiency), there is almost always a characteristic diastolic murmur; when such a

murmur is heard, the diagnosis is established with absolute certainty, no matter what the rest of the clinical or the hematologic picture may be.

Emboli are common. Small or large pieces of the polypous excrescences break off and are carried through the arterial stream to distant parts of the body, causing obliteration of capillaries, arterioles or even large arteries. In the capillaries and small arterioles, aneurysmal dilatation often takes place, the rupture of small aneurysms giving rise to hemorrhage wherever the rupture occurs, for instance, into the gastric cavity or into the subarchnoid space or some other portion of the brain. If the process occurs in the brain, there are outstanding symptoms of hemiplegia, meningitis or pachymeningitis. If the emboli lodge in the small peripheral vessels of the extremities, the symptoms simulate those of Raynaud's disease. Occasionally emboli occur in large vessels, such as the tibial vessels or the mesenteric or coronary vessels, completely obstructing the flow of blood to adjacent tissues, with resulting necrosis and gangrene of those tissues. Larger emboli may cause a saddle-shaped thrombus at the bifurcation of the aorta, obliterating the aorta. In protracted cases, there may be diffuse embolic nephritis instead of the focal embolic nephritis that is present in from 60 to 70 per cent of all cases. The fatal termination of such cases is usually the result of renal insufficiency, but no matter how marked the uremia, pericarditis is never present and the blood pressure is, as a rule, not elevated.

Examination of the peripheral blood, particularly from the ear, often shows macrophages. These are encountered in subacute bacterial endocarditis more than in any other severe infection.

In some cases, in which the predominant disturbances are in the hematopoietic system, there is marked secondary anemia, and the blood picture is similar to that of subleukemic leukemia, with from 15 to 20 per cent myelocytes and myeloblasts. In these cases the spleen is enormously enlarged, so that differential diagnosis between subacute bacterial endocarditis and myeloblastic leukemia is exceedingly difficult. In rare cases, the clinical picture simulates Banti's complex; that is, there is an immensely enlarged, hard spleen, and sometimes an enlarged liver, a hemorrhagic diathesis, leukopenia and mononucleosis are observed.

ACUTE STR. VIRIDANS ENDOCARDITIS

The most apparent symptom in all of the four cases to be reported was the septic type of temperature. The next most outstanding phenomenon was that in three of the four cases another readily demonstrable acute infection preceded the *Str. viridans* endocarditis.

Anemia was not present in any of the cases. For this reason, probably, percussion revealed no tenderness over the sternum. Extreme clubbing of the fingers was not seen, although in two cases there was slight

clubbing. Janeway's nodes were not present in any case. Petechiae occurred only two or three days before death and were not diffuse—a few were seen in the conjunctivae, some in the mouth and on the hard palate, and some on the chest. Petechiae were not seen in all of the cases.

The cardiac murmur was not as pronounced as in subacute bacterial endocarditis and was more changeable, probably because of the rapidly progressive lesion in the valve and in the mural endocardium. The heart rate was extremely rapid. In one case (case 2) the infection developed on the basis of a fibrillating disease of the mitral valve, which is extremely rare in the subacute cases.

The spleen was large and soft, as in sepsis.

There were no embolic phenomena in the peripheral or the deep blood vessels.

The blood count was not characteristic, although there was a tendency to leukocytosis. Remarkably, despite the severity of the disease, the staff cells were not increased in number. The blood culture in all cases was positive for *Str. viridans*. According to Hadjopolous,⁷ the bacteriologist at Beth Israel Hospital, the type encountered was *Str. viridans* mites alpha or faecalis, which in his opinion is of greater virulence than the type found in subacute bacterial endocarditis.

In the two cases that came to autopsy the valve was found to be ulcerated. It also showed the presence of very fresh polypous vegetations. In one case, in which the endocarditis was preceded by pneumonia, the polypous deposits were extremely small, the ulceration predominating. In this case there was one infarct in the spleen. In the other case, there were infarcts in the lungs only.

CASE 1.—History.—A man, aged 20, was admitted to the hospital on March 24, 1932, and died on April 5, 1932. At the time of admission, he had had a temperature of 102 F. and abdominal pain for one week. The pain had diminished, but the temperature continued to be elevated. The pulse rate was 103, and the blood pressure, 120 systolic and 50 diastolic.

The patient had poliomyelitis and scarlet fever in childhood, and acute rheumatic fever at the age of 16. After the attack of scarlet fever, his mother was told that he had valvular disease. However, his recovery was so complete that his uncle, a physician who saw him frequently, said that he was unable to detect any abnormal manifestations in the heart until the onset of the present illness.

Physical Examination.—The heart showed visible apex pulsation in the fifth left interspace, a presystolic thrill over the apex, a presystolic and a systolic murmur over the apex and a loud systolic murmur over the aortic region.

7. Hadjopolous, L. G., and Burbank, Reginald: Study on Streptococci in Relation to Pathogenicity and Sugar Fermenting Properties, *J. Lab. & Clin. Med.* **15**:539 (March) 1930.

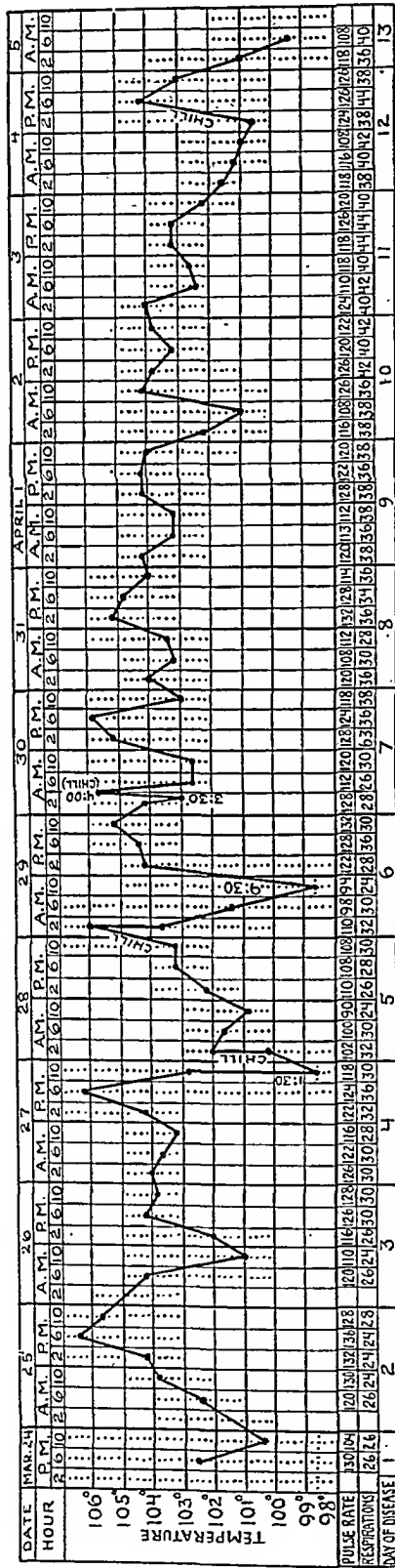


Chart 1.—Temperature chart for case 1.

The spleen was enlarged but not tender.

The liver was much enlarged. The right lobe extended to the umbilicus.

Laboratory Findings.—The electrocardiogram was normal.

The urine showed a faint trace of albumin but otherwise was normal.

The blood count showed: hemoglobin, 54 per cent; red cells, 4,800,000; white cells, 14,700; staff cells, 6 per cent; segmented cells, 33 per cent; polymorphonuclears, 77 per cent; mononuclears, 17 per cent; small lymphocytes, 10 per cent, and monocytes, 7 per cent. The sedimentation rate was 40 per cent.

The blood culture yielded *Str. viridans*.

Course.—During the patient's entire stay in the hospital, the temperature remained elevated, varying between 100 and 106 F., the rises in temperature always being preceded by repeated chills—a typical septic type of temperature (chart 1). The subjective complaints were headache, occasional vomiting and one nosebleed. Clubbing of the fingers developed during the period in the hospital. Petechiae appeared in the conjunctivae and over the thorax in the last two days of life. On the last day, the patient was icteric. The sensorium was clear to the end.

Comment.—Although we could not trace a recent acute infection in this case, the immediate infection was acute *Str. viridans* endocarditis of a truly septic type on the basis of a valve that had become chronically diseased as a result of scarlet fever in childhood.

CASE 2.—History.—Mrs. E. S., aged 51, was admitted to the hospital on May 29, 1932, and died on June 9, 1932. Seven days before admission she began to suffer from severe headache, fever, nausea, vomiting and general weakness. The temperature was 103 F. Three days later she had a chill after which the temperature rose to 105 F. Just before admission, the temperature rose to 107 F.

Twenty-one years prior to admission the patient noticed precordial pain, after which she experienced frequent attacks of pain in the joints. Thirteen years before she was confined to bed for almost two years, owing to cardiac and articular pains. During the past few years she had been troubled by cystitis and frequent and painful micturition. For the past year and a half she had seen black spots before her eyes. For a long time she had a well compensated mitral stenosis.

Physical Examination.—The patient was lying comfortably in bed, but complained of tenderness over the precordium. There were two pinpoint petechiae without white centers in the left conjunctiva, two small punctate purpuric spots on the right buccal mucous membrane and two punctate petechial spots with white centers in the upper portion of the left side of the chest, anteriorly and posteriorly. The blood pressure was 105 systolic and 65 diastolic.

The heart on percussion was enlarged and fibrillating. The rate was 100. There was a soft blowing murmur over the apex.

Laboratory Findings.—The roentgenogram of the chest was suggestive of mitral stenosis with decompensation. The roentgenogram of the kidneys was normal.

Urine obtained by cystoscopy contained colon bacilli as well as *Str. viridans* and much pus.

The blood count showed: hemoglobin, 50 per cent; red cells, 3,280,000; white cells, 10,900; staff cells, 23 per cent; segmented cells, 68 per cent; lymphocytes, 6 per cent; monocytes, 2 per cent, and metamyelocytes, 1 per cent. The sedimentation rate was 38 mm. Toxic degeneration of the cells was noted.

The first blood culture was sterile; the second showed three colonies of *Str. viridans*, and the third showed gram-negative bacilli in the broth and one colony of streptococci on the plate.

Course.—Until death, the patient had a septic type of temperature ranging from 101 to 106 F. The urine occasionally showed granular casts, much pus, a few red blood cells, many white blood cells and a four plus reaction to the benzidine test. During the cystoscopic examination, the patient complained of pain in the right costovertebral region. A diagnosis of right pyonephrosis with an obstructed ureter was considered. The trigon showed several submucous hemorrhages and slight trabeculation of the bladder. The patient's mental state was that of confusion and euphoria. She went rapidly downhill, became drowsy and had left facial weakness. The final stages of the illness seemed to indicate cerebral involvement. Fibrillation continued to the end. The spleen was definitely palpable. The patient died on the twelfth day after admission.

Autopsy (performed by Dr. Alfred Plaut).—The heart weighed 382 Gm. The pericardial sac was intact and contained a small amount of clear fluid. The subepicardial fat was very thick, covering most of the surface. There were no subepicardial hemorrhages. The pulmonary artery was free. The right auricle was considerably wider than is normal and was not hyperemic. The right ventricle was moderately distended. The valves of the right side of the heart were intact. The aortic valve was intact except for slight sclerosis at the base. There was considerable sclerosis of the sinus of Valsalva and of the ascending aorta. The mitral ostium was very narrow. When looked at from above through the very wide left antrum it seemed covered by a smooth ovoid protrusion, which was attached to the mitral valve near the septum. This large vegetation was soft and elastic. Its cut surface was clear and spongy. The valve was shortened. The chordae were short and thick. The atrial surface of the valve was covered with many small protrusions which formed a continuous layer. No lesions were seen in the endocardium of the atrium itself. A wart about 2 mm. high was situated on the tip of the posterior papillary muscle. The left ventricle was narrow, and the myocardium was dark brownish red. Laterally, near the atrioventricular curve, an ochre-colored area 3 cm. long was seen on the cut surface. The coronary arteries were moderately sclerotic. The right one was wider than the left.

Both lungs (weight, 990 Gm.) were large, light and emphysematous, with small hyperemic areas in the lower lobes. There was a flat scar in the apex of the left lung, and a small Ghon focus was seen in the lower lobe of the right lung. The arteries of the lungs were slightly arteriosclerotic.

The spleen was slightly enlarged. There were a few capsular thickenings. The organ was soft but not mushy—softer than is usual in subacute bacterial endocarditis and firmer than a septic spleen. It was dark red, and the markings were distinct.

Both kidneys peeled out of the capsule easily. They showed a few small conical abscesses in the cortex. There were no hemorrhages on the surface or on the cut surface. The renal pelves and the ureters were intact. The pelvis of the right kidney showed chronic pyelitis. The bladder was slightly trabeculated. Its mucosa was pale except for the trigon, which was moderately hyperemic. The urethra was very wide.

The results of microscopic examination were as follows: The large vegetation on the mitral valve consisted mainly of micro-organisms and fibrin. The pedicle was edematous and moderately infiltrated with leukocytes and mononuclear elements. The neighboring portion of the endocardium was practically without inflam-

mation. The left coronary artery, which appeared in four sections, was thick-walled, considerably calcified and surrounded by lymphocytic infiltration. The adjoining myocardium appeared normal. Another section from the mitral valve gave the picture of both old and recent endocarditis with much leukocytic infiltration. There were also heaps of bacteria (*Str. viridans*). There were small areas of calcification at the base of the valve.

The spleen showed much stasis. The centers of the follicles were partly hyalinized. The sclerosis of the vessels was slight. There were some large cells in the pulp, which had basophilic protoplasm and large, irregularly shaped nuclei.

The kidneys presented the classic picture of Löhlein's embolic focal glomerulonephritis. An infarct consisted mostly of necrotic kidney tissue, with the outlines of the tubules and the glomeruli fairly well preserved. Under the capsule and in the axis of the infarct many leukocytes were seen. In the routine slide, no accumulations of micro-organisms were conspicuous. Microscopic serial sections made from the block containing the metastatic renal lesion showed, near the apex of the triangle, a blood vessel which contained thick heaps of micro-organisms. Most of these were morphologically streptococcic. The organisms, however, did not retain the green stain. In some thinner slides colon bacilli also could be made out.

Comment.—This patient had a chronic, well compensated disease of the mitral valve (mitral stenosis and regurgitation). She also had recurrent pyelitis. On this occasion, she took sick with all the symptoms of left-sided pyelonephrosis. No additional signs or symptoms were present to awaken suspicion clinically that a superimposed acute bacterial endocarditis was present. The chills and fever, however, indicated the existence of sepsis, which we thought originally to be due to a focus in the kidney. The catheterized specimen of urine showed both colon bacilli and *Str. viridans*. Therefore we made a diagnosis of colon bacillus pyelonephrosis and acute *Str. viridans* endocarditis secondary to the primary infection. The presence of *Str. viridans* in the urine provided a clue to the diagnosis because it is well known that in *Str. viridans* endocarditis the organisms may pass through the kidneys with the urine, often so injuring the glomeruli as to cause focal embolic nephritis (Löhlein-Baehr), although they may also pass out with the urine without damaging the kidneys. In the course of an acute infection of an indeterminate nature, if *Str. viridans* is found in the urine, it provides the clue that the condition is *Str. viridans* septicemia.

CASE 3.—*History.*—L. G., a man, aged 41, was admitted to the hospital on March 14, 1933, and died on March 20, 1933. On admission, he complained principally of pain in the region of the liver, productive cough, substernal pain, dyspnea, chills and fever (temperature from 101 to 104 F.).

The patient came to the United States twenty-five years prior to admission. He had an attack of rheumatic fever ten years before admission, with swelling of the lower extremities up to the knees, which kept him in bed for six months and out of work for a year. Tonsillectomy was performed during that year. For fifteen years he had had a chronic cough productive of yellowish-white sputum, but no dyspnea or orthopnea was noted. Seven or eight months prior to admission he had an attack of pain radiating to the groin. Roentgen examination gave negative results. His physician stated that two weeks before admission he was icteric.

Eight days prior to admission the patient awoke with a sour taste in the mouth. He was seized with a burning substernal pain and a dull pain across the epigastrium. A druggist relieved the burning pain, but the epigastric pain remained, becoming localized in the right upper quadrant. A severe cough appeared, which was productive of light yellow sputum, never blood-streaked. After prolonged coughing there was slight substernal pain. Since the onset of this illness, the patient had been dyspneic and orthopneic, had had chills and fever (the temperature ranging between 101 and 104 F.) and had noticed that his urine was red.

Physical Examination.—At the time of admission the patient was a dyspneic, orthopneic, cyanotic man, with cardiac decompensation, coughing moderately and expectorating thin, mucopurulent material. The blood pressure was 102 systolic and 65 diastolic.

The pupils were very small and did not react to light or in accommodation. Exophthalmos was present.

The lungs were emphysematous. Numerous rhonchi were noted throughout, and there were many moist râles at the bases, extending rather high and heard in the axillae and anteriorly. There was slight dulness at the bases, with diminished breathing.

The apex of the heart was felt in the fifth interspace in the midclavicular line. A presystolic murmur was heard at the apex. The rate was 100, with regular sinus rhythm; the pulmonary second sound was louder than the aortic second sound.

The liver was felt five fingerbreadths below the costal margin. It was somewhat tender. The spleen was not felt. No ascites was present.

There were clubbing and cyanosis of the finger-tips and toes. A fine tremor was observed in the hands. No edema was present in the extremities.

Laboratory Findings.—A blood count, on March 14, showed: hemoglobin, 71 per cent; red cells, 3,790,000; white cells, 13,000; staff cells, 10 per cent; segmented cells, 70 per cent; polymorphonuclears, 80 per cent, and mononuclears, 20 per cent. The sedimentation rate was 27 mm. The venous pressure was 14 cm.

A blood culture on March 15 was sterile.

A serologic test for syphilis on March 15 gave a doubtful, nonspecific reaction, owing to the presence of pneumonia.

The urine, on March 15, showed: specific gravity, 1.020; an acid reaction; cloudiness; an orange color; no albumin; a few epithelial cells, and some crystals.

The icteric index, on March 15, was 7.

Roentgen examination of the chest, on March 15, gave the following results: There was intense congestion of the lungs. Numerous small patches of bronchopneumonia were diffusely scattered throughout the central portion of the right lung and about the root of the left lung. A small parietal effusion was noted in the lower portion of the right pleural cavity. The shape of the heart was characterized by marked accentuation of the curves of the right auricle and the right ventricle. The curves of the pulmonary artery and the left auricle were not prominent. The diagnosis was bronchopneumonia, purulent effusion, marked cardiac decompensation and mitral disease.

The heart rate, on March 16, was 110 per minute. An electrocardiogram showed: lead II, diphasic T waves, and lead III, negative T waves. It was interpreted as indicating sinus tachycardia with myocardial damage, possibly due to the influence of digitalis.

Course.—March 16: On the day after admission (March 15), the temperature rose to 104.6 F., but it came down to 101.2 F. on March 16. There were numerous rhonchi throughout the chest, with fine crepitant râles at the bases of both lungs. The patient's general condition was poor. He had pain in the rectum as a result of thrombosed hemorrhoids. Phlebotomy was performed, 250 cc. of blood being removed, which caused a slight improvement in the clinical picture. The venous pressure was 18 cm. before phlebotomy and 8 cm. afterward. The diagnosis was bronchopneumonia with cardiac decompensation. Only a systolic murmur was heard at the apex. There were clubbing and cyanosis of the finger-tips.

March 17: Expiratory difficulty was prominent. The temperature fell to 101 F.

March 20: The patient was very ill. Breathing was deep and regular; the respiratory rate was 34, and the pulse was of fair quality, bounding and easily compressible. The lungs were full of moist râles and rhonchi. The patient died.

Autopsy (performed by Dr. Alfred Plaut).—The heart weighed 390 Gm.; it was 11.5 by 10 by 7 cm. and of normal shape. The apex was formed by both ventricles. The subepicardial fat was thick. The mitral ostium was 10.5 cm. wide.

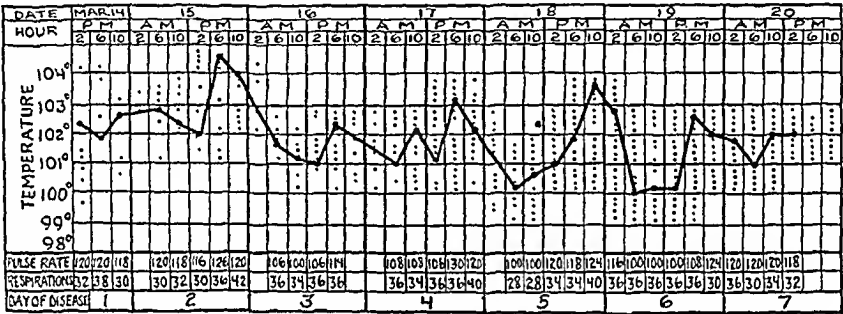


Chart 3.—Temperature chart for case 3.

The left auricle was slightly distended, and the left auricular appendage was narrow. The mitral valve throughout was the seat of old and recent endocarditis. The chordae were attached at the very edge. The webs were gone, but the chordae were only slightly thickened. The edge of the valve was dull, notably near the left edge of the heart. About two thirds of the valvular edge was covered by soft papillary masses which continued upward to the endocardium of the left auricle for nearly 2 cm. above the posterior cusp. The papillary muscles were moderately flattened and hypertrophic. The trabeculae of the left ventricle were more flattened. The left ventricular wall reached a thickness of 1.8 cm. The aortic leaflet was distinctly vascularized; the vessels could be seen with the naked eye up to about 1 cm. from the edge. The posterior leaflet was very short, and no vascularization could be seen in it. In the neighborhood of the auricular endocarditis, small gray, glassy, slightly elevated, round dots were seen in the endocardium. The aortic ostium was 8.5 cm. wide. The posterior cusp was very short. Its edge was rolled toward the wall of the aorta, and it bore a fine row of verrucae. The right cusp was less distorted; the rolling of the edge was conspicuous only in the region of the nodule, and only the posterior half of the cusp was covered with verrucae. The left cusp was slightly posterior. The commissures were drawn out, but only slightly dissociated. The ascending aorta was thin-walled and normal in width and showed much atheroma. The pulmonary ostium and the tricuspid ostium were

normal. The right auricle was slightly wider than normal, and the right auricular appendage was narrow and firm. The right ventricular wall, with trabeculae, reached a thickness of 7 mm. The myocardium was glassy and purplish, with a slight admixture of brown. No scars were seen. The right coronary artery was narrow throughout; the ostium was also narrow and was not surrounded by any scar formation. The left coronary artery was rather wide. The left circumflex branch continued nearly to the right edge of the heart posteriorly.

Both lungs were heavy. There were old adhesions over the upper portion of the upper lobe of the left lung, and some fibrinous layers were present over the whole upper lobe. Both lobes of the left lung were the seat of many confluent bronchopneumonic foci, most of which had completely coalesced. There were interlobar, recent adhesions. The bronchi and the blood vessels showed nothing unusual. There was a shallow scar in the apex. The hilar lymph nodes were anthracotic and soft. The right lung presented a similar picture. In the lower half of the lower lobe the pneumonic foci were more distinctly separated from each other. There was a scar in the right apex.

The thoracic aorta showed little atheroma.

The spleen was large (weight, 300 Gm.; dimensions, 13 by 10 by 5 cm.) and fairly firm. In the capsule, several small, firm, gray thickenings were seen. On the cut surface, numerous irregularly shaped follicles were prominent. The trabeculae were thin. The suprarenal glands were thin.

The left kidney weighed 215 Gm. and was 12.5 by 6 by 3 cm. The right kidney weighed 210 Gm. and was 12 by 6 by 3 cm. The capsules stripped with some difficulty. There were many indistinct, very shallow, purplish depressions, the outlines of which were similar to those of arteriosclerotic scars, although the depressions were much less deep than such scars generally are. The right kidney was the seat of a mixed infarct measuring 2 cm. at the base and 2 cm. in depth. The glomeruli were visible on the cut surface. The striation of the cortex was not very distinct but was normal as far as it was visible. The cortex was slightly wider than is normal. At some spots one had the impression that there might be a mild degree of infarction in small areas. No hemorrhages could be seen.

The results of microscopic examination were as follows:

The liver showed moderate central stasis.

In the kidneys, corresponding to the depressed spots, rather recent scars were seen, most of them showing large round cell infiltration. There were no sclerotic lesions. The glomeruli were cellular throughout, but most of them were intact. At several points characteristic Löhlein lesions were found. In some of them the process seemed to be one of necrosis without embolism.

In the spleen, the germ centers contained much hyalin. The pulp was hyperemic; there were not many leukocytes.

The lungs contained many heart disease cells.

Crush smears from the mitral valve showed cocci of varying sizes and shapes. There were many large involution forms. After treatment of the material with calcium carbonate, culture yielded pure *Str. viridans*.

The diagnosis was: old and recent mitral and aortic endocarditis with much destruction of the valves; a rheumatic lesion with superimposed bacterial endocarditis; mild dilatation and hypertrophy of the left ventricle; moderate hypertrophy of the right ventricle; swelling of the spleen, with large follicles; a mixed infarct in the right kidney; focal embolic glomerulonephritis (Löhlein); confluent bronchopneumonia of both lungs; scars in the apexes of both lungs; moderate arteriosclerosis of the abdominal aorta and its branches; fatty change in the liver; a small cavernous hemangioma in the right lobe of the liver, and hemorrhoids.

Comment.—Until two weeks before admission to the hospital this patient was well except for an old mitral stenosis. When he was taken ill the condition was correctly diagnosed as bronchopneumonia. During the course of the illness acute *Str. viridans* endocarditis developed, to which he succumbed within three weeks after the onset of the primary infection.

CASE 4.—*History.*—Mrs. R. W., aged 51, was admitted to the hospital on Nov. 29, 1931, and died on Jan. 11, 1932. On admission her chief complaints were: fever, weakness, prostration, chilly sensations, sweats and anorexia of twelve days' duration and pains on the right side of the head for seven days.

Two weeks before admission the patient began to feel tired, having malaise and a sticking sensation in the left tonsillar region. Two days later she had a temperature of 103 F., was markedly prostrated and complained chiefly of severe aching pains all over the body, especially in the back and the lower extremities. There were marked anorexia and chilly sensations followed by sweats, and the temperature fluctuated for five days between 101 and 105.2 F., being of the septic type. The temperature gradually came down as a result of lysis, but for the five days before admission it was constant between 100 and 103 F. There was marked amelioration of the symptoms so that the patient complained only of weakness, occasional chilly sensations, mild sweats, sharp lancinating pains in the right side of the head, dizziness and anorexia.

The patient had two living children, one aged 26 (with rheumatic cardiac disease) and one aged 23. In childhood she had measles and had her tonsils and adenoids removed. Hysterectomy and bilateral salpingo-oophorectomy were performed three years before for myoma uteri. She had had recurring attacks of left-sided paratonsillitis (two or three attacks yearly) for the past few years. She had occasionally had headaches. Presbyopia had existed for the past few years. Chronic progressive deafness had developed during the past twenty years. There had been no coughing, expectoration, hemoptysis or pain. At an examination for insurance twenty years before, a murmur was heard. There had been no dyspnea, orthopnea or edema. The patient had had marked constipation for many years. She suffered from extreme nervousness and insomnia and cried readily.

Physical Examination.—The patient was a rather pale, thin elderly woman, lying in bed. She was feverish.

The pupils reacted to light and in accommodation. The eyes showed no petechiae or changes in the fundi. The nose showed some scars, left by a previous operation; the mucosa was hypertrophied.

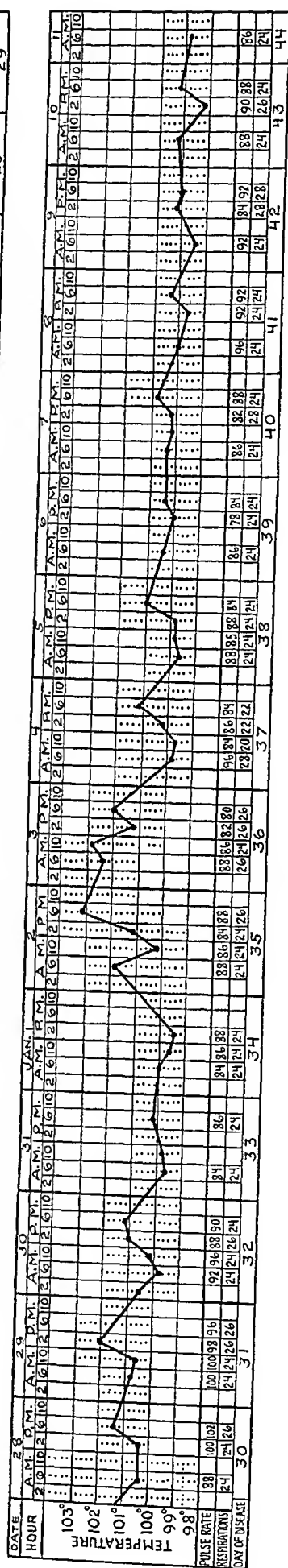
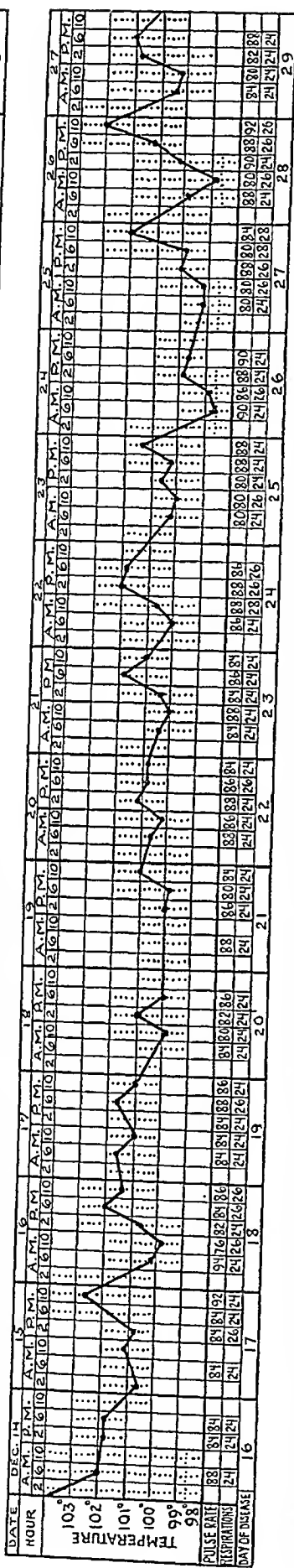
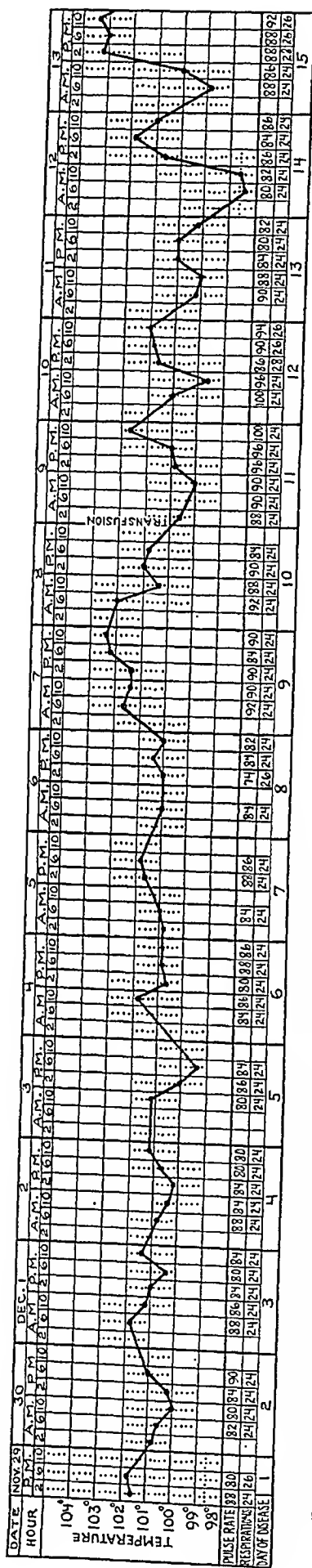
Both ear drums were markedly thickened, and hearing was greatly impaired. The tongue was moist and clean. The teeth were false. The pharynx was impacted. The tonsillar region was inflamed, and some caseous material was present in the right tonsillar fossa.

On examination of the heart, no thrills were felt. The maximum apex impulse was felt at the fifth interspace, in the midclavicular line. There was a short, harsh presystolic murmur at the apex. The pulmonic second sound was accentuated.

The chest, the abdomen and the extremities were normal.

Laboratory Findings.—The urine was normal, except for a faint trace of albumin.

The blood was normal except for slight secondary anemia and a slight increase in staff cells (from 16 to 21 per cent). The sedimentation rate was 31 mm.



Blood cultures showed: on Nov. 30, 1931, twenty colonies of *Str. viridans*; on December 3, sixty-three colonies of *Str. viridans* mites alpha; on December 10, sixty-six colonies of *Str. viridans*, and on December 18, *Str. viridans*.

The results of roentgen examination of the chest, on Nov. 30, 1931, were as follows: The lungs showed moderate emphysema but no infiltration or consolidation. The pleura of the lower lobe of the right lung was thickened. There was calcification of the lymph nodes at the root of the left lung. The heart was not enlarged. The aorta was not sclerotic or dilated.

Course.—The patient was given two transfusions of blood, but went progressively downhill. Toward the end she began to complain of severe pain in the left upper quadrant of the abdomen. She showed typical embolic phenomena in the extremities, and it was necessary to give her narcotics to relieve the pain. On the day of death she began to complain of substernal pain. A mixture of the hydrochlorides of the opium alkaloids was given. Half an hour later she died suddenly.

Comment.—This patient had chronic endocarditis of the mitral valve. She was subject to frequent sore throat, and for several weeks immediately before admission she suffered from a moderately severe sore throat. Since subacute bacterial endocarditis seldom sets in when sore throat is present, it is possible that the sore throat in this case was the expression of a septic tonsillar infection which predisposed the patient to acute fulminating *Str. viridans* endocarditis.

GENERAL COMMENT

In reviewing the four cases presented, two questions arise: Why is *Str. viridans*, ordinarily a nonpathogenic organism, pathogenic in certain cases, and why is *Str. viridans* endocarditis slowly progressive in the majority of cases and rapidly fatal in a few?

As a rule, the effect of a micro-organism depends on its virulence as well as on the resistance of the body, i. e., the existing immunity. The theory that under certain conditions a nonpathogenic organism can suddenly, by mutation, become virulent does not seem entirely plausible. It seems far more reasonable to assume that the increased virulence of an organism is due to the fact that some pathologic process has offered it a more favorable culture medium. That *Str. viridans* becomes virulent in this way is shown, we believe, not only by the fact that it can become pathogenic in a previously diseased endocardium but by the fact that it can become pathogenic when implanting itself in chronically diseased bile ducts, causing cholangitis lenta.

As to the factors that determine whether *Str. viridans* endocarditis will be rapidly fatal or slowly progressive, it is well known that in addition to lowered general immunity alteration in tissue immunity is important. A disturbance in local tissue reaction determines, in the first place, the possibility of cohesion between invading bacteria and the tissue. In bacteremia, although bacteria must necessarily pass through the cardiac

valves and the heart, bacterial invasion of normal valves or a normal heart is a great exception. Even in cases of severe sepsis in which multiple abscesses are found in the heart, the valves remain intact. Orth⁸ demonstrated this experimentally, as he was able to produce bacterial endocarditis by injecting bacteria intravenously only in rabbits in which the endocardium had been previously damaged.

When cohesion is possible, owing to loss of tissue reaction, the progress of the local pathologic change depends largely on the reactivity of the reticulo-endothelium. Whenever there is bacterial invasion of the blood, the main factor in the defense mechanism is the reticulo-endothelium of the liver, the spleen and the bone marrow, which first destroys and then absorbs the end-products of the micro-organisms without permitting damage to the parenchyma of the organs. This explains why, in the course of most infections, the liver and spleen are practically unaffected, except, possibly, for enlargement and softening of the spleen. The function of the reticulo-endothelium of the bone marrow, when there is bacterial invasion, is not only to destroy the invaders but to stimulate the leukoblastic apparatus so that in most cases leukocytosis with polymorphonucleosis develops, and occasionally also a considerable increase in immature white cells (staff cells).

Lexer⁹ recently furnished an explanation of why the reticulo-endothelium in the liver, spleen and bone marrow is so effective in absorbing the end-products of bacteria. By injecting a solution of india ink intravenously into rabbits, he was able to show that absorption is most rapid and most complete where the lumens of the capillaries are largest, namely, in the liver, the spleen and the bone marrow. Where the capillaries are of medium size, as in the kidneys and the lungs, absorption is not so rapid, and where they are smallest, as in the skin, absorption is almost negligible.

If the reactive power of the reticulo-endothelium is abnormally low, either because of its own deficiency or because of an overwhelming bacterial invasion, not only do the small and medium capillaries fail to react properly, but even the largest capillaries in the liver, spleen and bone marrow fail similarly. The result is multiple suppurative areas in the liver and even in the spleen; the loss of reactive function of the reticulo-endothelium of the bone marrow manifests itself as a disturbance in the leukoblastic element, so that there is marked reduction in the granulocytes, resulting in subgranulocythemia or possibly agranulo-

8. Orth, J.: Ueber die Aetiologie der experimentellen mycotischen Endocarditis, *Virchows Arch. f. path. Anat.* **103**:333, 1886.

9. Lexer, E.: Die autoplastische Deckung von Schädellücken aus dem Beckenkamm, *Deutsche Ztschr. f. Chir.* **239**:743 (Jan. 1) 1933.

cythemia. In the still more severe cases, erythropoiesis is likewise interfered with so that marked secondary anemia occurs. Occasionally the megakaryocytic activity also is disturbed, bringing about thrombocytopenia with hemorrhagic diathesis.

In cases of severe bacterial invasion, the reactive power of the reticulo-endothelium may be more disturbed in other parts of the body than in the liver, spleen and bone marrow, so that one finds thrombi in all of the middle-sized and small capillaries throughout the body, even in the skin. In some cases, the capillaries or the superficial arterioles of the skin become so blocked with thrombi as to cause large areas of cutaneous necrosis. When the condition continues for several days, the tissues supplied by the blood vessels undergo suppuration and necrosis, so that the smaller arterioles and capillaries may become soft and break; this explains multiple diffuse hemorrhage in severe cases of sepsis. In these cases, it is not arteritis or capillaritis which causes an obstruction to the flow of blood to the surrounding tissues, but actual blockage by thrombi that are the result of bacterial action on the walls of the vessels.

Siegmund¹⁰ and Dietrich,¹¹ on the basis of experimental and pathologic studies, classified the reactive power of the reticulo-endothelium to invading micro-organisms into three grades: (1) areactive, in which there is absolute loss of this power; (2) partially reactive, in which the function of the reticulo-endothelium is incomplete, and (3) reactive, in which the response is so favorable that the invaders are destroyed and their end-products absorbed.

It is important to keep in mind that the reaction of the reticulo-endothelium to bacterial invasion is not alike throughout the body. Only in the severest types of infection is the entire reticulo-endothelium reactive. In the vast majority of cases, the reticulo-endothelium is reactive in some parts, as in the liver, spleen and bone marrow, but partially reactive or areactive elsewhere. This would explain why in many cases cohesion between the invading micro-organisms and the tissue takes place only in certain parts of the body, giving rise to localized pathologic changes. If cohesion between bacteria and tissue is not to take place in any part of the body, there must be a generally reactive response of

10. Siegmund, H.: Untersuchungen über Immunität und Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**:114, 1923; Gefässveränderungen bei chronischer Streptokokkensepsis, Centralbl. f. allg. Path. u. path. Anat. **35**:276, 124; Zur Pathologie der chronischen Streptokokkensepsis, München. med. Wchnschr. **72**: 639, 1925.

11. Dietrich, A.: Die Reaktionsfähigkeit des Körpers bei septischen Erkrankungen in ihren pathologisch-anatomischen Aeusserungen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **37**:180, 1925.

the reticulo-endothelium of the entire body. In other words, the reactive reticulo-endothelium kills the bacteria and absorbs the end-products so completely as to allow no pathologic changes, or at most extremely insignificant changes. These mild changes may be inflammatory and lead eventually to healing. This is exemplified by those cases of acute general infection in which, although there are physical signs pointing to endocardial involvement, if the patient succumbs to the general infection the endocardium shows but slight inflammatory change. If the patient recovers, all endocardial signs disappear, as a rule, owing to complete healing. In some cases, of course, during the process of healing the inflammatory changes cause some deformity of the valve, as illustrated by chronic rheumatic or syphilitic valvular disease.

When there is only a partially reactive reticulo-endothelium, there is but partial interference with the destructive process of the bacteria. In subacute bacterial endocarditis, the reticulo-endothelium is only partially reactive; hence the inflammatory changes (polypous excrescences) in the endocardium. In many of these cases the reactive power of the reticulo-endothelium might still be sufficient to withstand the invasion and permit of recovery of the patient were it not for the location of the lesion. The location is not only one where the lesion is irremovable but one from which emboli can be carried readily through the blood stream to the most distant parts of the body to cause death. In other words, it is the consequences of this polypous type of bacterial endocarditis, in which the excrescences serve as a continuous focus of infection, that bring about the fatal termination.

In acute *Str. viridans* endocarditis, on the other hand, the reticulo-endothelium of the endocardium is no longer partially reactive but is areactive; in three of our four cases, this was the result of a severe, immediately preceding infection. The areactive reticulo-endothelium of the endocardium furnishes an exceedingly good culture medium for the invading micro-organism, so that the now very virulent *Str. viridans* can carry on its damaging activity with great rapidity, producing ulcerated areas on the endocardium and endocardial sepsis that runs quickly to a fatal conclusion.

CONCLUSIONS

1. *Str. viridans* may be the cause of acute, rapidly fatal endocarditis occurring on the basis of a previously diseased valve.

2. This form of endocarditis is usually preceded by some previous acute infection of several days', or at the most several weeks', duration. This was so in three of the four cases reported here. As the primary infection precedes the acute endocarditis by only a few days, it may so efface the symptoms of endocarditis as to make the diagnosis of acute

Str. viridans endocarditis impossible ante mortem, as in the case in which the condition was preceded by pneumonia. In all our cases, the symptoms of septicemia were in the foreground.

3. We believe that the reason why the cases reported had a rapidly fatal, instead of a protracted fatal, course, is that there was almost total loss of the reactive power of the reticulo-endothelium of the endocardium. A primary factor in the areactive quality of the reticulo-endothelium was an immediately preceding acute infection. Because the reticulo-endothelium of the endocardium was areactive, local inflammatory changes were minor and destructive changes maximal.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

V. CONDUCTIVITY, TOTAL BASE, CHLORIDE AND ACID-BASE EQUILIBRIUM

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AND

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Studies of the acid-base equilibrium of the plasma in pregnancy have been incomplete either because they were based on too few patients or because all of the various cations (sodium, potassium, calcium, magnesium or total base) and anions (Cl^- , HCO_3^- , HPO_4^- , SO_4^- , protein and organic acid) were not determined. Stander and his co-workers made a complete study of the acid-base equilibrium in three pregnant women. Oard and Peters made a similar study in twelve pregnant women, but omitted determinations of SO_4^- and organic acid. Numerous other reports of studies of the carbon dioxide content and, in a few instances, of p_{H} have been published, but the number of reports of total base in pregnancy is extremely small. However, similar reports on non-pregnant persons are also few and are based on a study of a relatively small number of subjects.

In table 1 are listed some of the published data for these various substances in nonpregnant and pregnant women. The average figure is given for the nonpregnant group. None of the investigators, so far as we know, have obtained their data from the same women for the different periods of pregnancy; therefore, the lowest average figure is given. In view of the marked changes in some of these substances associated with pregnancy and the inability of any one to explain the mechanism involved, the number of reports is surprisingly small.

The range for determined total base in the normal subject is from 147 to 161 millimols, with an average of 154, while in pregnancy the range is from 139 to 158 millimols, with an average of 147.

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TABLE 1.—*Reported Averages for Total Base, Conductivity, Carbon Dioxide Content, p_{H} and Serum Chlorides in Nonpregnant and Pregnant Persons*

	Number of Subjects	Total Base, mM.*	Conductivity as Sodium Chloride,†		Serum Sodium Chloride, mM.*	Carbon Dioxide, per Cent by Vol.	pH
			Per Cent	mM.*			
Nonpregnant							
Kramer and Tisdall..... (J. Biol. Chem. 53: 241, 1922)	10	153.0†
Briggs (J. Biol. Chem. 57: 351, 1923)	2	153.6†	102.5
Salvesen and Linder..... (J. Biol. Chem. 58: 617, 1924)	7	153.3†
Salvesen (Acta med. Scandinav. 69: 126, 1928)	6 F§	151.0	106.2	59.0	7.47
Kydd, Oard and Peters..... (J. Biol. Chem. 98: 241, 1932)	8 F	153.8	61.6	7.39
Peters et al. (J. Biol. Chem. 67: 141, 1926)	15	155.7	103.5	57.8
Stander et al. (J. Biol. Chem. 85: 233, 1929)	3 F	155.3	106.6	56.9	7.34
Atehley and Benedict..... (J. Clin. Investigation 9: 265, 1930)	10	151.9	103.5	65.0
Sunderman et al. (J. Clin. Investigation 3: 37, 1926)	8	154.7	133.0	104.0
Darrow and Hartmann..... (Am. J. Dis. Child. 37: 51, 1929)	13	150.7	100.0	55.3
Gram and Cullen..... (J. Biol. Chem. 57: 477, 1923)	0.799	136.7	103.3
Earle and Cullen..... (J. Biol. Chem. 83: 545, 1929)	78 F	64.0	7.45
Siedentopf and Eissner..... (Ztschr. f. Geburtsh. u. Gynäk. 97: 17, 1930)	23	7.37-7.40
Wirz (Arch. f. Gynäk. 139: 511, 1930)	16	7.46
Range		147-161	0.787-0.810		97-110	49-74	7.33-7.51
Average		154.0	0.799	134.8	103.7	64.0	7.4
Pregnant							
Michaelis, L. (Die Wasserstoffionen-Konzentration, Berlin, Julius Springer, 1914)	23	Alkaline
Hasselbach and Gameltott..... (Biochem. Ztschr. 68: 206, 1915)	8	Normal
Bock (Arch. f. Gynäk. 131: 468, 1928)	15	Acid
Krebs and Briggs..... (Am. J. Obst. & Gynee. 5: 67, 1923)	17	145.9†	99.9
Marraek and Boone..... (Brit. J. Exper. Path. 4: 261, 1923)	17	144.5†	100.9	53.8
Dennis and King..... (Am. J. Obst. & Gynee. 7: 253, 1924)	16	159.5†	96.9	48.8
Stander et al. ²	3	147.0	104.1	46.3	7.37
Kydd, Oard and Peters..... (J. Biol. Chem. 98: 241, 1932)	10	145.8	103.7	52.6	7.36
Gaebler and Rosene..... (Am. J. Obst. & Gynee. 15: 808, 1928)	32	48.0
Siedentopf and Eissner..... (Ztschr. f. Geburtsh. u. Gynäk. 97: 17, 1930)	95	7.45
Wirz (Arch. f. Gynäk. 139: 511, 1930)	30	7.49
Range		139-158	90-107	38-61	7.28-7.46
Average		147	101 (590 mg.%)	50.0	7.4

* mM. indicates milliequivalents per liter.

† The results are corrected for the depression of conductivity caused by serum protein.

‡ The sum of individual determinations of cations.

§ F indicates female subjects.

Chlorides in the normal subject range from 97 to 110 millimols, with an average of 103.7, while in pregnancy the range is from 90 to 107 millimols, with an average of 101.

The reports of the alkali reserve have been given both as carbon dioxide content and as bicarbonate. The normal carbon dioxide content of the blood ranges from 49 to 74, with an average of 64 per cent by volume, while in pregnancy the range is from 38 to 61, with an average of 50 per cent by volume. The figures for bicarbonate are usually about 3 per cent by volume lower. The alveolar and arterial carbon dioxide tensions in the normal resting person vary from 37 to 58, with an average of 40, while in pregnancy the average is 33 mm. of mercury.

A study of the reports of p_H in pregnancy seems to indicate that the change, if any, is toward the alkaline side. In a recent journal Kydd and his co-workers, basing their opinion on reports in the literature, especially on that of Stander (three determinations) and on their own study of ten pregnant women, stated that there is no change in p_H . Myers and his co-workers,¹ also basing their opinion on reports in the literature, especially on those of Gaebler and Rosene (fifty-six observations on thirty-two pregnant women), Siedentopf and Eissner (ninety-five observations on ninety-five pregnant women), and Wirz (thirty pregnant women), stated that the p_H is definitely increased toward the alkaline side. This citing of authorities by these two groups of investigators, with different interpretations, indicates a lack of study of the reported data by both. Thus, Gaebler and Rosene studied patients only during the last two months of pregnancy. Siedentopf had ninety-five observations on different women for the ten lunar months, thus including from one to twenty-eight patients in each group, and his conclusion is that the p_H is increased toward the alkaline side. However, if we divided his figures into three consecutive groups, which are large enough for statistical analysis, we find no change of any significance. It seems evident to us that these various investigators have disregarded the wide range of p_H found in normal persons as well as the hourly variations and have ascribed undue significance to the slight change found in pregnancy. Earle and Cullen stated that hourly determinations indicate that there are marked fluctuations of p_H , but that there is a general tendency for it to increase during the day. This increase ranges from p_H 0.01 to 0.07, the latter figure of which is greater than the reported increase in pregnancy. This controversy can be settled only by serial determinations of the carbon dioxide content and p_H in at least twenty women who are studied at frequent intervals during pregnancy.

1. Myers, V. C.; Muntwyler, E., and Bill, A. H.: Acid-Base Balance Disturbance of Pregnancy. *J. Biol. Chem.* **98**:253 (Oct.) 1932; Alleged Alkalosis in Pregnancy, *ibid.* **98**:267 (Oct.) 1932.

Serial studies of these various constituents were made by us on the same women during pregnancy and the puerperium to determine the change in the individual case. Figures for plasma volume, obtained with congo red, as described in previous articles, were available. Thus the total amounts of base and combined electrolyte (conductivity) could be calculated and the direction and degree of change determined.

METHOD

Blood was obtained in oiled syringes without stasis. A portion was injected under oil into centrifuge tubes. The clot was separated in all cases in from twenty to forty minutes, and after centrifugation the serum was removed and kept under oil. All determinations were made on this serum. For total base determinations, the Stadie-Ross method was used, but the proteins were first removed by precipitation with heat and acetic acid in a bomb, because digestion and ashing could then be carried out with less loss of base due to sputtering or creeping. Determinations of carbon dioxide content were made with the Van Slyke constant volume apparatus, using 1 cc. of serum. Determinations of p_H were made with the Hasting-Sendroy bicolorimetric method. Chlorides were determined with the Wilson-Ball modification of Van Slyke's method. The wheatstone-bridge of the Leed and Northrop student potentiometer, a microphone hummer as a source of high frequency current, a resistance box and earphones were used for the determination of the conductivity. The cell was a special one made by Leed and Northrop, requiring approximately 2 cc. of serum, and could be sealed to prevent loss of carbon dioxide. All readings were made at 20 C. The instrument was calibrated with known solutions of sodium chloride and was checked on numerous occasions. The average of a number of readings was always taken, and we believe that this measurement of serum electrolytes is far more exact than the determinations of total base. Corrections were made, the Gram formula for the depression caused by the proteins being used.

$$C_c = \frac{C_o \times 100}{100 - (d \times p)}$$

C_o = observed conductivity
(as percentage of
sodium chloride)

p = serum protein

C_c = corrected

d = 2.2, Gram's factor
for depression caused
by 1 per cent protein

Conversion of the percentage of sodium chloride to millimols and the multiplication of the latter figure by the factor, 1.16, gives a value which is essentially equal to the total base. As has been stated, the patients designated as series A, were followed throughout pregnancy and the puerperium. Another group, series B, was studied from term to eight weeks post partum, and the total group is composed of the fore-

going and many for whom single determinations were made. Plasma volumes were determined in all cases, and the multiplication of the volume by any of the substances determined gave the total amount of this substance in the circulation. We admit that we cannot determine the true plasma volume, but we believe, and have advanced proof in previous articles, that consistent results can be obtained. Since all determinations were made by one person, with a carefully controlled technic, we believed that variations in the total amounts are of significance.

In table 2 is listed the conductivity, expressed as percentage of sodium chloride, for the different periods. The average for the normal

TABLE 2.—*Conductivity of the Serum in Percentage of Sodium Chloride: Variations and Averages in Pregnancy and the Puerperium*

Percentage	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.740-0.749.....	1	4
0.750-0.759.....	2	5	2
0.760-0.769.....	2	2	3	12	6	3	1	..
0.770-0.779.....	5	2	8	12	3	10	3	..
0.780-0.789.....	10	3	5	14	8	9	4	4
0.790-0.799.....	3	1	4	4	4	5	..	1
0.800-0.810.....	1	2	3	1	1	1	1	4
Total.....	23	10	24	52	24	28	9	9
Means								
Total cases.....	0.780 ± 0.002	0.780 ± 0.002	0.773 ± 0.001	0.791 ± 0.002	0.782 ± 0.001		
Standard deviation....	0.012	0.015	0.014	0.014	0.01		
Series A.....	0.780	0.786	0.782	0.771	0.776	0.775		
Series B.....	0.771	0.774	0.780	0.790	0.795
Normal range: 0.787-0.810 per cent; 134.5-138.4 millimols								

nonpregnant person is 0.800 per cent. It is evident that there is a definite decrease of the total electrolytes in pregnancy, reaching a minimum of 0.771 per cent at term, and that it requires at least from six to eight weeks after delivery before the conductivity is again normal. Statistical calculations indicate that the mean at term, compared with the normal mean and also with the mean for from ten to fifteen days post partum, demonstrates that the changes are of significance. This decrease in conductivity, meaning a decrease in the total electrolyte (serum ash), is at variance with the statement made by Stander and Tyler² that the plasma ash remains normal during pregnancy. Their failure to detect significant changes is due to the fact that the method used by them is not sufficiently sensitive.

2. Stander, H. J., and Tyler, M.: Moisture and Ash of Maternal and Foetal Blood. Surg., Gynec. & Obst. **31**:276 (Sept.) 1920.

In table 3 are listed the conductivities expressed as grams of sodium chloride per kilogram of body weight. These figures were obtained by multiplying the plasma volume by the percentage of sodium chloride and

TABLE 3.—*Conductivity of the Serum as Grams of Sodium Chloride per Kilogram of Body Weight: Variations and Averages in Pregnancy and the Puerperium*

Gm. per Kg.	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.25-0.29.....	4	1	2	5	..	1
0.30-0.34.....	5	1	5	7	7	8	2	1
0.35-0.39.....	7	3	10	17	6	10	1	5
0.40-0.44.....	4	4	4	16	7	2	2	3
0.45-0.49.....	3	1	1	5	4	4	2	..
0.50-0.54.....	1	2	..	3	2	..
Total.....	23	10	23	52	24	28	9	9
Means								
Total cases..	0.364 ± 0.009	0.37 ± 0.008	0.384 ± 0.006	0.387 ± 0.005	0.386 ± 0.009		
Standard deviation....	0.067	0.057	0.061	0.057	0.070		
Series A.....	0.34	0.38	0.36	0.36	0.36	0.40		
Series B.....	0.39	0.36	0.39	0.44	0.38

TABLE 4.—*Total Base, Millimols: Variations and Averages in Pregnancy and the Puerperium*

Millimols	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
140-144.....	2	1	..	9	1	4	1	..
145-149.....	1	3	6	8	4	3	1	2
150-154.....	6	4	11	14	5	5	1	1
155-159.....	9	..	5	8	4	11	4	2
160-164.....	2	..	1	3	1	4	1	1
165-170.....	1	1	2
Total.....	21	8	23	42	16	27	8	8
Means								
Total cases.....	154.6 ± 0.8	152.2 ± 0.6	150.6 ± 0.6	152.9 ± 1.0	153.5 ± 0.8		
Standard deviation....	5.9	4.1	6.0	6.2	6.4		
Series A.....	156	150	152	154	151		
Series B.....	148	152	162	...	158
Normal range: 147-161 millimols								

dividing the product by the body weight. These data demonstrate that the total electrolyte in pregnancy, if calculated on a weight basis, shows no significant change.

In table 4 are listed the data for total base. The range is wide, but the relatively small standard deviations indicate that the majority of the figures fall between 145 and 160. The decrease at term is significant. Oard and Peters, in an attempt to account for this decrease, which they

stated amounts to approximately 8 millimols, ascribed 3 millimols to the decrease in serum protein, citing the work of Plass and his co-workers as proof of the lowered proteins. However, serial determinations of serum protein in pregnancy indicate a reduction which will account for approximately from 0.5 to 1.5 millimols, instead of the 3 millimols postulated by them. In a previous article³ we have indicated certain errors in the work of Plass and his co-workers and have also demonstrated that the change in serum protein in pregnancy is not as great as heretofore reported. Furthermore, Oard and Peters' conclusions are based on twelve determinations, which is too small a number for any consideration. There is a definite decrease in total base, amounting to from 4 to 6 millimols, which probably can be accounted for in part by the decrease in protein and bicarbonate, but a portion is unaccounted

TABLE 5.—Average Changes in Conductivity (as Sodium Chloride) and Total Base, Calculated on Total Amount Variations, Using the Initial Determination as One Hundred Per Cent for the Antepartum Period

	Conductivity		Total Base	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
From 26 to 35 weeks of gestation				
Average increase for all patients	16	16.8	15	18.0
Average increase for those showing increase.....	10	30.4	11	26.1
Average decrease for those showing decrease.....	4	21.3	2	9.5
No change	2	0	2	0
From 36 to 40 weeks of gestation				
Average increase for all patients	14	22.7	12	20.6
Average increase for those showing increase.....	10	32.4	12	20.6
Average decrease for those showing decrease.....	1	7.0	0	0
No change	3	0	0	0

for, and it is most important that no satisfactory explanation has been given for any of these changes.

In table 5 are listed the average changes in variations in the total amount of the conductivity and total base. These figures were obtained by the following calculations: The plasma volume is multiplied by the conductivity or total base, and the product is the total amount. The first determination is then assumed to be 100 per cent, and all subsequent readings are divided by this one, thus converting all figures to percentage of increase or decrease, making it possible to compare changes in different persons. At thirty weeks' gestation the majority of the patients had an increase of 17 per cent both in conductivity and in total base. At term all of the patients, with but one exception, showed an increase of 21 per cent in total base. The average increase in the conductivity was 23 per cent, with only one patient showing a decrease. It is evident that there is a definite increase in the total amount of both the anions

3. Dieckmann, W. J., and Wegner, C. R.: Studies of the Blood in Normal Pregnancy: IV. Percentages and Grams per Kilogram of Serum Protein and Fibrin and Variations in Total Amount of Each, Arch. Int. Med., to be published.

and the cations of the plasma in pregnancy. This is due, of course, to the increase in plasma volume and the necessity of maintaining osmotic equilibrium.

In table 6 are listed the changes in conductivity and total base, calculated on the total amount for the puerperium. The determination

TABLE 6.—Average Changes in Conductivity (as Sodium Chloride) and Total Base, Calculated on Total Amount Variations, Using the Last Antepartum Determination as One Hundred Per Cent for the Postpartum Period

	Conductivity		Total Base	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
From 2 to 6 days post partum				
Average decrease for all patients	23	8.9	14	14.0
Average decrease for those showing decrease.....	12	19.5	10	20.0
Average increase for those showing increase.....	2	16.0	1	7.0
No change	9	0	3	0
From 10 to 25 days post partum				
Average decrease for all patients	33	5.7	28	1.4
Average decrease for those showing decrease.....	22	15.2	15	14.5
Average increase for those showing increase.....	6	23.2	5	21.0
No change	5	0	8	0
From 8 to 17 weeks post partum				
Average decrease for all patients	9	13.2	5	8.0
Average decrease for those showing decrease.....	8	15.5	3	12.7
Average increase for those showing increase.....	1	6.0	0	0
No change	0	0	2	0

TABLE 7.—Carbon Dioxide Content, Per Cent by Volume per Hundred Cubic Centimeters of Serum: Variations and Averages in Pregnancy and the Puerperium

Per Cent by Volume per 100 Cc. of Serum	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
40-44.....	3	..	1
45-49.....	1	1	2	7	3	1
50-54.....	5	3	3	9	4	5	1	1
55-59.....	4	3	6	22	10	16	6	..
60-64.....	1	2	1
Total.....	10	7	11	42	19	24	7	1
	Means							
Total cases.....	53	53	54	53	54	55	55	50
Series A.....	54	..	55	53	58	54		
Series B.....	52	54	54		

Normal range: 49-75 per cent by volume

at term was assumed to be 100 per cent, which was used as the divisor. The majority of the patients showed decreases in the total amount of plasma electrolyte after delivery, but the decrease was not as great as the increase during pregnancy. The probable explanation lies in the fact that many of these patients weighed more after delivery, thus requiring a larger volume of plasma, and the concentration of these substances increased as they returned to normal.

In table 7 are listed the variations and averages for the carbon dioxide content. Unfortunately, while the number of determinations

is large, few patients were followed throughout pregnancy. The figures for the averages at the different periods show little variation, thus again demonstrating the fallacy of studying groups rather than the same subjects at different times. It is evident from the determination of the carbon dioxide content that no marked acidosis exists in pregnancy.

TABLE 8.—Variations and Averages of p_H in Pregnancy and the Puerperium

p_H	Number of Patients						
	Ante Partum, Weeks				Post Partum, Days		
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26
7.30-7.34.....	2
7.35-7.39.....	3	2	3	14	4	7	..
7.40-7.44.....	6	2	4	18	7	12	4
7.45-7.47.....	1	1
Total.....	9	4	7	33	12	19	6
Means							
Total cases.....	7.40	7.39	7.39	7.39	7.39	7.39	7.37
Series A.....	7.40	7.39	7.38			
Series B.....	7.40	7.39	7.39	

TABLE 9.—Sodium Chloride Milligrams per Hundred Cubic Centimeters: Variations and Averages in Pregnancy and the Puerperium

Mg. per 100 Cc.	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
560-579.....	2	..	1	5	4	..	2	1
580-589.....	1	..	1	3	1	3	2	2
590-599.....	7	3	2	14	9	6	4	1
600-609.....	2	2	8	5	5	5	1	..
610-619.....	12	4	9	16	6	17	..	3
620-639.....	..	2	3	11	..	2	..	3
Total.....	24	11	24	54	25	33	9	10
Means								
Total cases.....	603.3 ± 1.6	607.3 ± 1.6	605.1 ± 1.5	597.3 ± 1.7	607.2 ± 1.3		
Standard deviation....	13.0	11.8	15.7	12.8	11.1		
Series A.....	604	605	609	612	595	602		
Series B.....	596	594	612	593	606
Normal range: 567-643 mg. per 100 cc.; 97-110 millimols								

In table 8 are listed the variations and averages for the p_H . Too few patients were followed throughout pregnancy, but the large number of determinations, all within normal limits, demonstrate definitely that no acidosis exists. The normal p_H , together with the decrease in carbon dioxide content and bicarbonate, indicates that a condition of compensated alkali or carbon dioxide deficit exists. It is most unfortunate that more determinations of p_H were not made in series A, because only serial observations can settle definitely the controversy as to

TABLE 10.—Data on Patients Followed Throughout Pregnancy and the Puerperium (Series A)

Patient, Gravida,* Color,* Age	Period of Gestation or Post Partum	Conductivity as Sodium Chloride			Plasma Volume Change, per Cent	Total Base		Sodium Chloride, Mg. per 100 Ce.	Carbon Dioxide, per Cent by Vol.		pH
		Per Cent	Gm. per Kg.	Change, per Cent		Change, per Cent	mM.†				
I	13 wks.	0.792	0.32	158	619	
II	29 wks.	0.794	0.44	167	166	159	151	603	
W	40 wks.	0.746	0.48	194	206	197	151	7.37	
20	12 days	0.776	0.54	94	90	93	156	607	..	7.40	
2	14 wks.	0.792	0.30	158	619	
I	30 wks.	0.794	0.33	115	115	105	145	619	
W	40 wks.	0.783	0.34	117	119	116	154	625	50	
23	12 days	0.783	0.32	87	86	81	143	619	58	
3	15 wks.	0.781	0.44	159	590	
I	30 wks.	0.768	0.47	123	125	116	147	603	
W	40 wks.	0.775	0.42	115	116	115	158	613	
25	12 days	0.783	0.46	92	91	89	155	601	
4	14 wks.	0.782	0.25	153	619	
VII	27 wks.	0.783	0.31	122	122	122	153	603	
W	40 wks.	0.752	0.35	128	133	619	
30	14 days	0.768	0.28	76	75	84	157	586	
5	12 wks.	0.780	0.31	155	613	
II	28 wks.	0.774	0.36	128	129	125	150	603	
W	39 wks.	0.764	0.38	137	140	136	151	
25	14 days	0.770	0.54	124	123	128	157	581	55	7.37	
6	14 wks.	0.774	0.37	161	613	
I	27 wks.	0.769	0.39	124	125	114	147	619	
W	40 wks.	0.774	0.38	141	141	137	156	619	56	7.37	
19	11 days	94	86	144	619	56	7.40	
7	14 wks.	0.778	0.25	158	595	55	7.40	
VI	30 wks.	0.787	0.26	111	110	110	158	590	50	
W	40 wks.	0.780	0.26	113	112	107	151	586	56	7.40	
31	5 days	0.782	0.31	103	103	107	157	589	56	7.37	
	13 days	0.765	0.38	125	127	130	154	585	58	7.40	
8	14 wks.	0.773	0.36	154	613	
III	28 wks.	0.793	0.30	94	92	89	150	589	
C	40 wks.	0.795	0.31	102	100	90	153	613	51	7.40	
30	11 days	85	619	57	7.37	
9	14 wks.	0.761	0.38	160	596	53	7.40	
I	29 wks.	127	122	...	619	
C	40 wks.	0.774	0.42	131	129	92	151	619	
21	3 days	0.780	0.43	95	94	89	147	601	
	12 days	0.783	0.44	93	92	...	147	596	58	7.40	
10	20 wks.	0.784	0.35	137	596	51	
I	36 wks.	0.770	0.37	110	113	125	152	555	
W	3 days	0.766	0.35	88	88	93	150	596	60	7.40	
26											
11	15 wks.	0.778	0.40	157	619	
I	28 wks.	0.802	0.38	105	102	97	149	619	55	7.37	
W	39 wks.	0.765	0.35	100	102	101	155	625	46	7.40	
22	12 days	0.762	0.37	93	94	91	150	590	55	7.40	
12	9 wks.	0.789	0.40	151	560	53	
I	27 wks.	0.775	0.49	131	133	128	145	625	50	
C	40 wks.	0.768	0.28	99	102	101	149	625	56	
28	11 days	0.776	0.32	99	98	99	151	601	57	
13	11 wks.	152	596	
VIII	29 wks.	0.774	0.39	...	106	106	152	613	
C	40 wks.	0.768	0.38	93	99	92	140	619	54	7.35	
37	11 days	92	95	144	607	55	7.40	
22	16 wks.	0.788	0.42	149	613	
II	28 wks.	0.773	0.34	93	95	...	149	613	53	7.40	
W	40 wks.	0.784	152	625	
24	12 days	0.781	0.34	151	619	

* W = white; C = colored.

† mM. = millimols.

whether the p_H in pregnancy increases toward the alkaline side or shows no significant change. From repeated observations of p_H since 1925, we believe that in normal pregnancy no significant changes occur, and, furthermore, that it will require repeated determinations on the same patients throughout pregnancy to prove a change.

TABLE 11.—Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Conductivity as Sodium Chloride			Plasma Volume Change, per Cent	Total Base		Sodium Chloride, Mg. per 100 Ce.	Carbon Dioxide, per Cent by Vol.	p_H
		Per Cent	Gm. per Kg.	Change, per Cent		Change, per Cent	mM.†			
31	39 wks.	0.768	0.46	619	46	7.40
I	12 days	64	...	164	613	60	7.40
C	8 wks.	74
15										
32	40 wks.	0.736	0.38	590	56	7.40
I	3 days	0.770	0.34	81	77	590	57	7.37
W	12 days	0.774	0.60	135	82	..	157	590	58	7.40
27	8 wks.	0.782	0.35	87	82	...	170	589
33	40 wks.	0.785	0.29	158	625	58
II	3 days	0.785	0.33	98	98	89	144	607	49
W	19 days	0.787	0.31	89	89	91	161	589
29	9 wks.	0.802	0.36	106	104	104	158	625
34	40 wks.	0.803	0.40	153	619
I	5 days	0.705	0.33	71	72	79	168	619	54	7.40
C	8 wks.	0.803	0.39	88	88	86	149	630
25										
35	36 wks.	0.782	0.36	131	590	54
II	11 days	0.770	0.35	87	88	110	164	619	50	7.37
W	8 wks.	0.783	0.35	84	84	613
24										
36	40 wks.	0.768	0.35	543	42
I	3 days	0.768	0.42	110	110	590	35
C	12 days	0.782	0.37	88	86	619	53
25	8 wks.	100	589
37	38 wks.	0.775	0.46	137	619	56
III	12 days	0.793	0.32	61	60	619	45
W	8 wks.	0.800	0.44	88	85	93	149	595
30										
39	39 wks.	0.759	0.40	543	53
I	11 days	0.785	0.33	69	67	613	59
W	17 wks.	0.814	0.31	63	59	...	157	625
17										
40	40 wks.	0.763	0.41	147	590
IV	3 days	0.763	0.45	96	96	96	146	578
C	25 days	0.784	0.49	102	100	104	153	596
28	8 wks.	0.790	0.40	85	82	96	172	613	50
43	38 wks.	0.775	0.40	159	625
V	5 days	0.766	0.32	70	71	67	151	578
C	19 days	0.800	0.52	113	110	100	144	595
17	8 wks.	0.789	0.40	87	86	83	154	578

* W = white; C = colored.

† mM. = millimols.

In table 9 are listed the variations and averages for serum sodium chloride. The variation is marked, but the averages show little change, with the exception of the first week post partum, when there is a slight decrease, amounting to from 10 to 15 mg. Harding and Van Wyck⁴

4. Harding, V. J., and Van Wyck, H. B.: Diet in Treatment of Pre-Eclampsia, J. Obst. & Gynec. Brit. Emp. 33:17, 1926.

stated that the whole blood chlorides increase from the normal of 475 mg. per hundred cubic centimeters to a maximum of 518 mg. at the eighth lunar month, and then decrease to 490 mg. at term. Their results are based on a study of sixty-seven determinations. Our results, based on several hundred determinations, many of them on the same patients at different periods, indicate that there are no significant changes in the serum chlorides.

In table 10 are listed essential data for series A. The majority of the patients show a decrease in the conductivity and total base of the serum during pregnancy, which is most marked at term. Variations in total amount of these substances demonstrate definite increases, and calculation of each on a per kilogram basis also shows an increase, thus indicating that there is apparently an actual retention. The degree of change in total conductivity, total base and plasma volume is remarkably constant—a further proof of the fine balance maintained by the body. Carbon dioxide content and p_{H} determinations, while comparatively few, demonstrate that there is no acidosis in pregnancy. Serum chlorides show a wide fluctuation but no characteristic changes.

In table 11 are listed essential data for series B. In this group the observations extend from term to eight weeks post partum. Determinations of conductivity indicate a return to the normal at from six to eight weeks post partum. Observations on total base show such marked variations that no conclusions can be drawn. Variations in total amount show a decrease, and again they are of the same degree and direction as the changes in plasma volume. Determinations of carbon dioxide content, p_{H} and serum chloride are within the normal range.

CONCLUSIONS

The data for conductivity, total base, carbon dioxide content, p_{H} and chlorides, which have been reported in the literature for both normal nonpregnant and pregnant women, are based on a relatively small number of determinations. As a result, considerable confusion has arisen as to what changes, if any, occur in some of these constituents of the blood in pregnancy.

Determinations of these substances and, in addition, of plasma volume were made on various patients for the different periods of pregnancy. Similar studies were made on the same women by means of serial determinations at periodic intervals. The results were studied statistically, and the following conclusions are made: 1. The conductivity of the serum is decreased, reaching a minimum at term which is from 4 to 6 millimols below the normal, and it does not return to the normal until six to eight weeks post partum. This decrease, mean-

ing a decrease in the total electrolyte, predicates a decrease in the serum ash.

2. The conductivity expressed as grams of sodium chloride per kilogram shows no significant change.

3. The total base is decreased, reaching a minimum at term which is from 4 to 6 millimols below the normal. It does not return to the normal until two or three weeks post partum. The decrease in the total base is substantiated by the decrease in the conductivity, which can be determined more accurately than the total base.

4. The carbon dioxide content is decreased from 6 to 10 per cent by volume in pregnancy.

5. There are no significant changes of the p_H from the normal.

6. There is no acidosis of pregnancy, but the condition is one of a compensated alkali or carbon dioxide deficit.

7. Determinations for serum chloride show no significant change from the normal.

8. Variations in total amount of conductivity, expressed as percentage of sodium chloride and of total base, show an average increase at from twenty-six to thirty-five weeks of 16.8 and 18 per cent, respectively, and at term the average increases are 22.7 and 20.6 per cent. The increase in the individual cases is of the same magnitude as the plasma volume.

9. Similar studies with the addition of determinations of electrolyte metabolism on the same women during pregnancy are necessary before the mechanism of these various changes will be known.

10. A logical explanation of the decrease of electrolytes, serum protein, hematocrit values, etc., in pregnancy will be of inestimable value in solving many of the problems associated with edema.

STUDIES OF THE BLOOD IN NORMAL PREGNANCY

VI. PLASMA CHOLESTEROL IN MILLIGRAMS PER HUNDRED CUBIC CENTIMETERS, GRAMS PER KILOGRAM AND VARIATIONS IN TOTAL AMOUNT

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Although many of the reports of determinations indicate that cholesterol is increased in pregnancy, there is still lack of agreement as to the time when the increase begins, the amount and the cause of the gain. Greater importance is being ascribed to cholesterol, as shown by the constantly increasing number of papers on this subject in the literature. It is not known just what part it plays in the permeability of membranes, edema, nephritis, nephroses, pregnancy, resistance to infection, epilepsy, etc., but sufficient data have been accumulated to indicate that a marked change in cholesterol is intimately associated with these conditions, which undoubtedly are either the cause or the result of the change.

Cholesterol is found in both the erythrocytes and the plasma, occurring as the free alcohol and also as the ester of the fatty acids. In addition, certain other combinations or adsorption products of cholesterol and serum protein have been described. A noteworthy fact is that in the new-born baby cholesterol is present only in the free form.

In table 1 are listed data for plasma and whole blood total cholesterol (free and combined) in nonpregnant and pregnant women. The range for plasma cholesterol in the nonpregnant woman is from 80 to 250 mg. per hundred cubic centimeters, with an average of 175 mg., and for whole blood it is from 98 to 250 mg., with an average of 184 mg. In pregnancy the range for plasma is from 130 to 426 mg. per hundred cubic centimeters, with an average of 234 mg., while the range for whole blood is from 84 to 640 mg. with an average of 241 mg.

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The variations in the amount of cholesterol are extremely wide, and several explanations are possible: (1) Exact methods have been perfected only recently; (2) cholesterol may show rather wide variations hourly; (3) long continued alterations in diet may cause changes, and

TABLE 1.—*Reported Averages for Total Cholesterol in Nonpregnant and Pregnant Persons**

	Year	Nonpregnant			Pregnant		
		No. of Determinations	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	No. of Determinations	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.
Herrmann and Neumann..... (Biochem. Ztschr. 43: 47 1912)	1912	..	130-170	144	181
Klinkert (Berl. klin. Wehnsehr. 50: 820, 1913)	1913	17	130-275 P†	182	17	186-426 P	263
Bloor and Knudson..... (J. Biol. Chem. 29: 7, 1917)	1917	6	184-208	193	3	181-250-291	240
Siemons and Curtis..... (Am. J. Obst. & Gynec. 75: 569, 1917)	1917	18	200-380	260
Denis (J. Biol. Chem. 29-30: 93, 1917)	1917	6	185-250	214	9	183-283	236 (no change)
Pribram (Arch. f. Gynäk. 119-120: 57, 1923)	1923	15	84-640	252
Siemons and Stander..... (Bull. Johns Hopkins Hosp. 34: 7, 1923)	1923	..	(200-250)‡	...	24	190-330	190
Bunker and Mundell..... (J. A. M. A. 83: 836, 1924)	1924	..	(140-170)	...	72	155-220	190
Tyler and Underhill..... (J. Biol. Chem. 66: 1, 1925)	1925	10	180-249	207	100	140-338	261
Moynihan (Brit. M. J. 1: 393, 1925)	1925	..	133-192 P	130-260 P	Increased
Oser and Karr..... (Arch. Int. Med. 36: 507, 1925)	1925	18	105-246 P	187	6	200-300 P	260
Rosen and Krasnow..... (Am. J. Obst. & Gynec. 14: 321, 1927)	1932	27	153-201	171±16	91	139-326	193
Okey and Boyden..... (J. Biol. Chem. 72: 261, 1927)	1927	16	98-185	149
Boyd and Roy (India)..... (Indian J. M. Research 15: 643, 1928)	1927	..	82-184 P
McClure and Huntsinger..... (J. Biol. Chem. 76: 1, 1928)	1928	20	103-186	130
Gardner and Gainsborough.... (Lancet 1: 603, 1929)	1929	21	80-230 P	133	32	140-285 P	233
McEachern and Gilmour..... (Canad. M. A. J. 26: 30 and 158, 1932)	1932	90	130-200 P	161	12	173-269	217
Gray and McGee..... (Arch. Neurol. & Psychiat. 28: 357, 1932)	1932	29 M§	155-234	194±2.7 S.D. 22
Bruger and Somack..... (J. Biol. Chem. 97: 23, 1932)	1932	15	172-259	208

* Determinations were made on whole blood.

† P denotes plasma.

‡ Parentheses indicates that the figures are assumed by the authors.

§ M denotes male.

|| S.D. indicates standard deviation.

(4) with only one exception, all studies have been made on various groups of women for the different periods of pregnancy.

Bruger and Somack have shown, by hourly analyses of plasma cholesterol over a four-hour fasting period in nine normal subjects, that the standard deviation is ± 3.9 per cent, with limits of from ± 1.8

to ± 6.8 per cent. Similar determinations on whole blood were made every two hours for twenty-four hours in nine patients on standard diets, who were bedridden for various conditions. The cholesterol varied by a standard deviation of ± 8 per cent, with limits of variation of from ± 5.2 to ± 13.1 per cent. The data indicate that the higher the initial cholesterol level, the greater is the variation, but the standard deviations were practically the same for all cases. The ingestion of food had no constant effect, either immediate or late, on the cholesterol content of the blood.

McEachern and Gilmour made cholesterol determinations on whole blood on twenty-eight normal fasting persons. Blood was taken every hour for five hours. The standard deviation for their results, as calculated by Bruger and Somack, was ± 9.5 per cent, with limits of from ± 3.4 to ± 16.5 per cent. The authors concluded that such wide variations render single or haphazard studies of blood cholesterol of doubtful value. No evidence of cholesterol adsorption or of effect on the blood level was noted in twelve normal persons who were given large doses by mouth. A seasonal variation in the blood cholesterol of normal persons does not exist.

Gardner and Gainsborough,¹ who have carried out the most complete studies so far reported on cholesterol metabolism, concluded that during periods of fasting the cholesterol content of the plasma varies markedly in different healthy persons but is fairly constant in the subject himself; a single meal will cause no change, but prolonged diets, high or low in sterols, will cause variations in the cholesterol. The free cholesterol remains fairly constant, but the cholesterol ester shows the greatest changes. During the digestive process changes in the cholesterol content of the plasma occur frequently, at times as an increase and sometimes as a decrease, compared with the values during periods of fasting. Often a marked temporary disturbance of the ratio of the ester to the total cholesterol is observed. These peculiar changes must be regarded as evidence of an active endogenous metabolism, in which cholesterol takes part during digestion. The ester usually forms from 60 to 70 per cent of the total cholesterol.

Gray and McGee, who have made a study of cholesterol in normal, feeble-minded and epileptic patients, reported that in the same subject the difference between two cholesterol determinations must be at least 40 mg. per hundred cubic centimeters to be considered of any significance and that meals affected the cholesterol only to a moderate degree.

McClure and Huntsinger determined whole blood cholesterol at hourly intervals in normal subjects before and after various meals.

1. Gardner, J. A., and Gainsborough, H.: *Biochem. J.* **19**:667, 1925; **21**:130, 1927; *Quart. J. Med.* **23**:465, 1930.

They concluded that the ingestion of all foods causes an increase in cholesterol, but that the gain is in a descending order for the foods listed: olive oil and oleic acid, dextrose and egg albumin. Hourly studies on the fasting subject show no marked changes, but determinations on the same subject at weekly or monthly intervals may demonstrate significant changes.

Thus, a study of the reports on cholesterol indicates that it remains fairly constant in the subject himself, although the range is rather great, and that it is not affected by food unless prolonged alterations in diet are maintained. For the individual subject, the change in cholesterol, to be of any significance, should be at least 40 mg. per hundred cubic centimeters.

Moynihan, in 1925, reported the work of Shiskins which indicated that the cholesterol was increased approximately 30 per cent just preceding and during the first one or two days of the menstrual period.

Okey and Boyden, who made over two hundred serial analyses of whole blood cholesterols during periods of fasting, covering twenty-six monthly cycles in sixteen women, concluded that the most striking and consistent cyclic alteration observed in the lipid content of the blood was the fall in blood cholesterol, which took place almost invariably during or within a few days of the menstrual period. This was usually preceded or followed by levels for blood cholesterol which were higher than the averages for the persons concerned. Since the initial rise in the cholesterol level, the menstrual fall and the postmenstrual rise, with the secondary fall to approximately the average level, require two weeks or more for completion, it will be seen that the level for blood cholesterol in women is to be considered as a variable rather than a constant factor. Thus, cholesterol is subjected to additional influences in women because of the cyclic changes of the endocrine glands, and the range is thereby increased.

The wide ranges for the averages in pregnancy, listed in table 1, indicate that this condition produces even more marked alterations.

Kehrer,² basing his opinion on the reports of two investigators, concluded that in pregnancy there is a hypercholesteremia which begins in the third month and increases as the pregnancy progresses. He stated that the increased amount of cholesterol explains the fact that pregnant women require less ether or chloroform than nonpregnant women (the absorption of these anesthetics is increased by the high levels of lipid).

Denecke,³ also basing his opinion on essentially the same authors as Kehrer, concluded that the free and ester cholesterol of the blood

2. Kehrer, E., quoted in Halban, Joseph, and Seitz, Ludwig: *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenberg, 1926, vol. 6, p. 813.

3. Denecke, G., quoted in Hinselmann, H.: *Die Eklampsie*, Bonn, Friedrich Cohen, 1924.

are increased in pregnancy, owing to a decreased excretion in the bile. After delivery they are excreted rapidly in the milk, urine and bile, and by the end of the second week post partum the cholesterol level is normal.

Tyler and Underhill determined whole blood cholesterol in normal persons, and in pregnant women. They studied ten women in each month of pregnancy, beginning with the third, and reported that cholesterol and ester cholesterol increase gradually until term; at that time each is roughly one-third higher than at three months.

McEachern and Gilmour determined whole blood cholesterol in twelve pregnant women and concluded that a marked elevation is found in about 30 per cent of normal pregnant women, beginning about the sixth week prior to delivery, and that about 80 per cent have a level above normal on the first day after delivery. The figures are still high on the twelfth day post partum.

Gardner and Gainsborough made two or more serial determinations of total, free and ester cholesterol in eight women during pregnancy and one or more postpartum analyses in ten women, and concluded: 1. The free cholesterol of the plasma increases during pregnancy up to a maximum at about the thirtieth week; concurrently, the ester cholesterol falls to a minimum at about the same time. 2. From the thirtieth week, more or less approximately, the amount of free cholesterol decreases, and the ester cholesterol increases until an almost normal ratio of free to ester cholesterol is attained before or near parturition. 3. The values for plasma cholesterol are generally normal in the first week or two of the puerperium. 4. Some cases show a definite total hypercholesteremia in which the figures for total cholesterol run, roughly, parallel to the values for free cholesterol. During pregnancy there is a marked disturbance of the cholesterol metabolism, which results in great changes in the ratio of free to ester cholesterol in the plasma, but in less definite changes in the total cholesterol.

All of the investigators, with the exception of Denis who determined the blood cholesterol in nine pregnant women and stated that no increase was found, concluded that cholesterol is increased late in pregnancy, and many of them assumed that the increase is due either to a faulty elimination by the liver or to a retention preparatory for lactation.

METHOD

Determinations of plasma cholesterol and plasma volume, as described previously, were made on a number of women during pregnancy and the puerperium. One group, in which serial determinations were made on the same women during pregnancy and the puerperium, is designated as series A. A second group, designated as series B, was followed from term to eight weeks post partum. The total number of

cases includes both series, with the addition of many single analyses. The determinations for cholesterol were made on plasma which had been obtained as previously described. Leiboff's method was used. Only total cholesterol could be determined because of the volume of work, but it was believed that if changes did occur, either in free or in ester cholesterol, they would be of sufficient magnitude to affect the total.

In table 2 are listed the variations and means for plasma cholesterol during pregnancy and the puerperium. The difference between the means of the total cases for the first trimester and for term is signifi-

TABLE 2.—*Plasma Cholesterol, Milligrams per Hundred Cubic Centimeters: Variations and Means in Pregnancy and the Puerperium*

Range, Mg. per 100 Cc.	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
125-199.....	5	1	1	5	2	3	1	2
200-249.....	4	3	4	7	2	8	5	2
250-299.....	5	2	4	4	4	3	3	3
300-349.....	6	2	9	11	7	6	1	1
350-399.....	2	1	3	12	3	1	..	1
400-449.....	1	..	2	5	3	5	1	..
450-549.....	5	..	2
Total.....	23	9	23	49	21	28	11	9
Means								
Total cases.....	269.5 ± 11	307.6 ± 8.9	331.1 ± 9.4	310.7 ± 11.3	307.1 ± 10.6		
Standard deviation....	78.5	63.5	97.0	76.5	102.5		
Series A.....	263	...	289	268	...	248		
Series B.....	348	334	338	282	254

cant, amounting to an increase of 23 per cent. The slight variation for series A is due to the relatively small number of patients and to the marked individual variations. Series B shows a decrease of 27 per cent at eight weeks post partum. Our data, calculated either as the increase in the number of high cholesterol or as averages, demonstrate definitely that pregnancy is characterized by a hypercholesteremia, and that this condition not only begins early in pregnancy but is still present eight weeks post partum.

In table 3 are listed the variations and means for the grams of cholesterol per kilogram. The plasma volume multiplied by the milligrams of cholesterol per hundred cubic centimeters, and the product divided by the body weight equals the grams of cholesterol per kilogram. The increase is even more striking and at term amounts to 33 per cent, while at eight weeks post partum there is a decrease amounting to 39 per cent.

In table 4 are listed the changes in the percentage of total circulating cholesterol during pregnancy and the puerperium. The total cholesterol was determined by multiplying the plasma volume by the milligrams of cholesterol per hundred cubic centimeters. The first determination

TABLE 3.—*Plasma Cholesterol, Grams per Kilogram: Variations and Means in Pregnancy and the Puerperium*

Range, Gm. per Kg.	Number of Patients							
	Ante Partum, Weeks				Post Partum, Days			
	10 to 15	16 to 25	26 to 35	36 to Term	2 to 6	10 to 15	18 to 26	8 to 17 Weeks
0.070-0.099.	7	..	2	5	2	4	2	3
0.100-0.149.	13	4	11	14	8	12	7	3
0.150-0.199.	3	2	7	17	10	9	1	4
0.200-0.249.	2	..	3	4	1	2
0.250-0.300.	7	..	1
Total.	25	6	23	47	21	28	10	10
Means								
Total cases.	0.123 ± 0.006	..	0.148 ± 0.006	0.169 ± 0.006	0.151 ± 0.005	0.146 ± 0.007
Standard deviation	0.041	..	0.039	0.063	0.036	0.051
Series A.	0.118	..	0.136	0.130	0.167	0.129
Series B.	0.178	..	0.152	0.131	0.126

TABLE 4.—*Average Changes in Plasma Cholesterol Calculated on the Basis of Total Amount**

	Ante Partum				Post Partum					
	26-35 Weeks		36-40 Weeks		2-6 Days		10-25 Days		8-17 Weeks	
	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent	No. of Cases	Change, per Cent
Average increase for all patients....	13	33.9	14	27.9
Average increase for those showing increase.....	8	62.8	9	55.8	6	28.8	7	36.7	1	40.0
Average decrease for all patients....	19	11.8	35	15.0	10	21.2
Average decrease for those showing decrease.....	2	35.5	5	22.4	9	44.2	23	34.1	8	31.2
No change... ..	3	0	0	0	4	0	5	0	1	0

* The initial determination is used as 100 per cent for the antepartum period, and the last antepartum determination as 100 per cent for the postpartum period.

was assumed to be 100 per cent, and all others during pregnancy were divided by it and the dividend multiplied by 100. Determinations after delivery were converted similarly, using the figure found at term as the divisor. Thus all data were converted to a common factor and could be compared. At from twenty-six to thirty-five weeks' gestation there was an average increase of 33.9 per cent in cholesterol. At term the average increase was 27.9 per cent. Five cases showed an increase of 55.8 per cent, and five, a decrease of 22.4 per cent. Changes of ± 4 per

TABLE 5.—Data on Patients Followed Throughout Pregnancy and the Puerperium
(Series A)

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Plasma Cholesterol				Plasma Volume Change, per Cent
		Mg. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	
1	13 wks.	333	0.134	6.22
II	29 wks.	370	0.206	11.49	185	166
W	40 wks.	303	0.196	11.68	188	206
20	12 days	222	0.153	7.72	66	90
2	14 wks.	158	0.060	4.64
I	30 wks.	233	0.097	7.85	169	115
W	40 wks.	158	0.068	5.50	119	119
23	12 days	143	0.059	4.32	79	86
3	15 wks.	345	0.193	10.27
I	30 wks.	345	0.210	12.83	125	125
W	40 wks.	238	0.129	8.19	80	116
23	12 days	333	0.197	10.45	128	91
4	14 wks.	150	0.049	4.51
VII	27 wks.	333	0.133	12.22	271	122
W	40 wks.	150	0.069	6.00	133	133
30	14 days	75
5	12 wks.	333	0.133	7.11
II	28 wks.	263	0.122	7.25	102	129
W	39 wks.	140
25	14 days	123
6	14 wks.
I	27 wks.	338	0.170	9.32	...	125
W	40 wks.	218	0.107	6.77	73	141
19	11 days	230	0.119	6.69	99	94
7	14 wks.	266	0.086	9.19
VI	30 wks.	370	0.124	14.00	152	110
W	40 wks.	385	0.130	14.95	168	112
31	5 days	357	0.142	14.28	96	103
	13 days	380	0.187	18.76	125	127
8	14 wks.	434	0.202	18.74
III	28 wks.	200	0.076	7.90	42	92
C	40 wks.	353	0.139	15.18	81	100
30	11 days	85
9	14 wks.	239	0.120	5.98
I	29 wks.	194	0.105	6.15	103	127
C	40 wks.	312	0.168	10.08	169	129
21	3 days	326	0.178	9.93	99	94
	12 days	302	0.170	8.95	89	92
10	20 wks.	333	0.149	10.67
I	36 wks.	372	0.177	13.39	125	113
W	3 days	337	0.152	10.72	80	88
26						
11	15 wks.	238	0.122	8.19
I	28 wks.	313	0.149	11.01	134	102
W	39 wks.	333	0.153	11.71	143	102
22	12 days	250	0.121	8.25	70	94
12	9 wks.	150	0.075	4.61
I	27 wks.	133
C	40 wks.	333	0.121	10.45	227	102
28	11 days	272	0.111	8.37	80	98
13	11 wks.	244	0.128	8.73
VIII	29 wks.	200	0.101	7.62	87	106
C	40 wks.	194	0.097	6.90	79	99
37	11 days	224	0.113	7.39	107	92
22	16 wks.
II	28 wks.	312	0.139	8.91	...	95
W	40 wks.	150
24	12 days	128	0.056	3.38	38	93

* W denotes white race; C, colored race.

cent were listed as "no change." After delivery there was a constant decrease amounting to 21.2 per cent at eight weeks, which is not quite equal to the increase.

In table 5 are listed essential data for series A. Despite the marked fluctuations of cholesterol there was an average increase of 33 per cent

TABLE 6.—Data on Patients Followed from Term to Eight Weeks Post Partum (Series B)

Patient, Gravida, Color,* Age	Period of Gestation or Post Partum	Plasma Cholesterol				Plasma Volume Change, per Cent
		Mg. per 100 Cc.	Gm. per Kg.	Total Amount, Gm.	Change, per Cent	
31	39 wks.	361	0.216	14.44
I	12 days	174	0.079	4.46	31	64
C	8 wks.	74
15						
32	40 wks.	357	0.183	11.90
I	3 days	357	0.159	9.20	77	77
W	12 days	435	0.215	11.93	100	82
27	8 wks.	333	0.150	9.08	76	82
33	40 wks.	410	0.154	15.90
II	3 days	432	0.182	16.42	103	98
W	19 days	277	0.109	9.57	60	89
29	9 wks.	384	0.174	15.50	97	104
34	40 wks.
I	5 days	72
C	8 wks.	158	0.078	5.01	...	88
25						
35	36 wks.	381	0.176	12.01
II	11 days	500	0.226	13.91	116	88
W	8 wks.	345	0.156	9.16	76	84
24						
36	40 wks.	303	0.140	9.58
I	3 days	333	0.184	11.59	121	110
C	12 days	200	0.096	5.44	57	86
25	8 wks.	166	0.096	5.25	55	100
37	38 wks.	476	0.233	23.23
III	12 days	416	0.166	12.15	52	60
W	8 wks.	278	0.154	11.55	50	85
30						
39	39 wks.	333
I	11 days	303	0.127	6.57	...	67
W	17 wks.	238	0.091	4.54	69	59
17						
40	40 wks.	154	0.084	4.52
IV	3 days	238	0.139	6.72	149	96
C	25 days	294	0.184	8.60	190	100
28	8 wks.	263	0.134	6.33	140	82
43	38 wks.	361	0.186	13.40
V	5 days	411	0.170	10.82	81	71
O	19 days	223	0.146	9.09	68	110
17	8 wks.	200	0.103	6.35	47	86

* W denotes white race; C, colored race.

at term, with two patients showing no change. Further analysis of the data shows that there was an increase of 50 per cent in five patients and a decrease of 17 per cent in five. At twelve days post partum the values are still well above normal. The majority of the patients showed marked gains in total cholesterol and decreases at twelve days post partum. These changes in total cholesterol, suggesting a definite storage, indicate its importance but give no clue as to the reason.

In table 6 are listed essential data for series B. Marked fluctuations occur, but the tendency is for the values to decrease. The decrease in total cholesterol is of particular significance in that it indicates that the pregnancy was the stimulus for the increase.

COMMENT

What is the need for an increase in cholesterol in pregnancy? Is it a storage preparatory for lactation; is it a retention due to impaired elimination, or is it another manifestation of the disturbance in the chemical equilibrium of the blood caused by pregnancy? Pribram and others concluded that the increase is associated with a decreased excretion in the bile. However, we find the increase occurring early in pregnancy and persisting for weeks after delivery, which facts are not in accordance with the foregoing statement. Our findings, especially the persistence post partum, the irregularity in the amount of retention and the relatively small amount retained, would indicate that the increase is not a preliminary step in the preparation for lactation, as suggested by Slemmons and Stander. If the tissue retention is of the same magnitude as the blood retention it is possible that the storage of cholesterol is necessary for lactation. To prove this point, studies of metabolism are necessary.

It seems to us that the same mechanism which is causing a decrease in serum protein analogous to nephritis and nephroses, a decrease in the carbon dioxide content analogous to diabetes, and an increase in fibrin—all of which conditions are associated with hypercholesteremia—causes the increase in cholesterol in pregnancy. Whether or not it exercises a protective influence cannot be determined. We have found a marked hypocholesteremia in patients who died because of severe vomiting of pregnancy and of puerperal infection. In both conditions, because of the starvation (high fat and protein) and damage to the liver one would expect a hypercholesteremia. Further investigations are necessary before the changes can be explained.

CONCLUSIONS

In individual subjects, both plasma and whole blood cholesterol remain fairly constant, although within rather wide limits, and they are not affected by food unless prolonged alterations in diet are maintained.

Determinations of plasma cholesterol and plasma volume were made on various groups of women and also on the same women for the different periods of pregnancy. The following conclusions are warranted: 1. The variations and range of cholesterol in the same woman during pregnancy may be tremendous. The majority show an increase, which is apparent at from ten to fifteen weeks' gestation.

2. There is an average increase of 23 per cent at term and a decrease of 27 per cent at eight weeks post partum.

3. Cholesterol calculated as grams per kilogram shows an increase of 33 per cent at term, and a decrease of 39 per cent at eight weeks post partum.

Variations in the total amount of cholesterol indicate an increase of 33.9 per cent at from twenty-six to thirty-five weeks of gestation, and an increase of 27.9 per cent at term. After delivery there is a constant decrease, amounting to 21.2 per cent at eight weeks post partum.

The increase in both the concentration and the total amount of cholesterol is probably not preparatory for lactation but is associated with other changes in the chemical equilibrium, which is so markedly disturbed in pregnancy. Further work is necessary to determine whether the increase in cholesterol in pregnancy is caused directly by the pregnancy or is the result of the other changes in the blood.

CONSTANCY OF IRON IN THE BLOOD PLASMA AND URINE IN HEALTH AND IN ANEMIA

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Clinical studies on the production of hemoglobin following the oral administration of iron indicate the physiologic activity of this substance in hypochromic anemia. Heath and his co-workers¹ have shown that in such patients the intramuscular injection of ferric ammonium citrate is followed by a rise in hemoglobin representing approximately a quantitative reappearance of the injected iron as hemoglobin. Their observations suggest that the action of iron on the production of hemoglobin is not vaguely "catalytic" but bears a quantitative relationship to the formation of hemoglobin. The interest of investigators is, therefore, logically directed to the question of absorption of iron, since the degree of absorption of a given iron compound obviously controls the amount of iron available for the regeneration of hemoglobin.

Unless complete experiments on iron balance are performed, studies of absorption based on the elimination of iron in the feces are profitless. This is due to the fact that in patients given large doses of iron by mouth the small amounts absorbed must be distinguished from the large amounts which pass unchanged through the intestinal tract. Furthermore, since iron is secreted into the intestinal contents, it is difficult to differentiate between nonabsorbed iron and that secreted into the intestinal tract from the body. It was thought, however, to be worth while to determine whether, following the oral administration of iron, this substance was increased in the plasma or the urine. It was decided also to study the urine to determine whether during periods of production of hemoglobin in anemic patients the iron over and above that converted into hemoglobin appeared in the urine. Since the amount of iron present in the blood plasma and the urine would of necessity be small, the pri-

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1. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anaemia, *J. Clin. Investigation* **11**:1293, 1932.

mary essential was the development of a method which was sufficiently accurate to be applicable to the relatively small samples which could be secured from anemic patients.

CHEMICAL METHODS

Glassware.—All apparatus was rendered free from iron by preliminary extraction with hydrochloric acid. In the interval between experiments, the apparatus was thoroughly washed with soap and water, rinsed with tap water, and finally rinsed with iron-free distilled water.

Reagents.—The reagents employed were: distilled water, redistilled in glass vessels; concentrated sulphuric acid, iron-free; potassium thiocyanate, highest purity, 10 per cent solution in iron-free distilled water; ethyl acetate, highest purity; standard iron wire (99.9 per cent pure iron), and trichloroacetic acid, highest purity.

All reagents were submitted to analysis by the same procedure as that used in the determination of the iron content of the blood plasma and the urine. The maximum iron content permitted was always less than the experimental error of the method (0.002 mg.).

Standard Iron Solution for Determinations with Blood Plasma and Urine.—One hundred milligrams of metallic iron in the form of research purity iron wire was weighed and brought into solution with the smallest possible amount of iron-free concentrated hydrochloric acid, one part of acid to one part of distilled water being used. The solution was transferred quantitatively to a 1,000 cc. volumetric flask and diluted to volume. From this solution two standards were prepared. For the standard for urinalysis exactly 10 cc. of the stock solution was transferred to a 1,000 cc. flask, 10 cc. of concentrated sulphuric acid was added, and the contents were diluted to volume with distilled water. One cubic centimeter of this solution was equivalent to 0.001 mg. of iron. For the standard for analysis of blood plasma, 100 cc. of the stock solution was transferred to a 1,000 cc. flask, 10 cc. of sulphuric acid was added, and the contents were diluted to volume with distilled water. One cubic centimeter of this solution was equivalent to 0.01 mg. of iron.

PROCEDURE FOR ANALYSIS OF THE BLOOD

Five cubic centimeters of venous blood was drawn in a chemically clean glass syringe and transferred to a centrifuge tube to which one drop of a saturated solution of potassium oxalate had been added and dried. The blood was stirred gently with a glass rod and centrifugated at approximately 1,600 revolutions per minute for ten minutes. The plasma was then tested spectroscopically and discarded if evidence of hemoglobin was present.

Six cubic centimeters of distilled water was added to exactly 2 cc. of this plasma and thoroughly mixed. Two cubic centimeters of a 20 per cent solution of trichloroacetic acid was added, shaken, and allowed to stand at least ten minutes. The resulting mixture was filtered on ashless filter paper. To exactly 5 cc. of filtrate in a 300 cc. Kjeldahl flask, 2 cc. of concentrated sulphuric acid and two small glass beads were added. The solution was then digested in the usual manner until about 0.5 cc. of colorless liquid remained in the flask. To exactly 1 and 2 cc. of standard iron solution were added 7 and 8 cc. of distilled water, respectively. After thorough mixing, 2 cc. of a 20 per cent solution of trichloroacetic acid was added to each sample, which was then shaken and allowed to stand at least ten minutes. The standards were then digested in the same way as the

sample of blood plasma. After digestion was complete, the contents of the flasks were allowed to cool and the inside of each flask was carefully washed down with 20 cc. of hot distilled water. The contents of the flasks were thoroughly shaken, held at the boiling point for a few moments and allowed to cool. Into each flask 10 cc. of a 10 per cent solution of potassium thiocyanate was added. The contents of the flasks were shaken thoroughly and transferred immediately to 50 cc. volumetric flasks, each containing 10 cc. of ethyl acetate. The contents were shaken and diluted to the mark with distilled water. After the contents were shaken again, the ethyl acetate was allowed to layer out, and portions were removed by individual pipets to the cups of a microcolorimeter and compared with the standard iron solution set at 10 or 20.

PROCEDURE FOR URINALYSIS

All specimens of urine were collected directly into glass containers, and 1 cc. of concentrated sulphuric acid was added to each container with the one or two hour collections, and 2 cc. of acid, to each container with the twenty-four hour collections. This precaution was taken to preclude the possibility of an increasing alkalinity precipitating the iron from solution. The containers were thoroughly shaken before the samples were removed for analysis.

To 100 cc. of urine in a 300 cc. Kjeldahl flask, 10 cc. of iron-free concentrated sulphuric acid and two small glass beads were added. To two of the 300 cc. Kjeldahl flasks were transferred 5 and 10 cc. of the standard iron solutions equivalent to 0.005 and 0.01 mg. of iron, respectively. Ten cubic centimeters of concentrated sulphuric acid and two small glass beads were added. Sufficient distilled water was added to make the total volume 60 cc. The samples and standards were digested in the usual manner. The digestion was continued until about 0.5 cc. of colorless liquid remained. The contents of the flask were cooled, and the inside of each flask carefully washed down with hot, distilled water; the contents were then thoroughly shaken and held at the boiling point for a few moments. The contents were again cooled, and 10 cc. of 10 per cent potassium thiocyanate solution added to each flask. After being shaken thoroughly, the contents were transferred rapidly to 100 cc. volumetric flasks containing 10 cc. of ethyl acetate each. They were shaken thoroughly and diluted to the mark with distilled water. They were again shaken, and the layers of ethyl acetate were removed by individual pipets to the cups of a microcolorimeter. The standard was set at 10.

Accuracy of Method.—From a study of recoveries from solutions of iron in distilled water, blood plasma and urine, it has been found that the lower limit of accuracy of this modified thiocyanate method is 0.002 mg. of iron.

EXPERIMENTAL PROCEDURES

The Blood Plasma Iron Content.—The observations recorded here are based on a study of the iron content of the plasma of five normal persons, of three patients suffering from anemia due to chronic loss of blood with achlorhydria and of two patients with pernicious anemia. The general results of the investigations are given in the table.

Blood was taken from a normal man immediately before the oral administration of 6 Gm. of ferric ammonium citrate, and subsequent samples, three, seven and eleven hours afterward. Chart 1 illustrates the entirely negative effect of the ingestion of the compound on the

Results of Experimental Study

Case	Type of Anemia	Blood Condition (Control Period)			Amount of Iron and Ammonium Citrate per Day	Blood Condition (Treatment Period)			Reticulocytes at Peak of Their Response to Iron, per Cent
		Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per C.Mm.	Plasma Iron, Mg. per 100 Cc.		Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per C.Mm.	Plasma Iron, Mg. per 100 Cc.	
Controls	Five normal persons without anemia	15.6	4.5 to 5.5	0.47*	None	15.6	4.5 to 5.5	0.47*	...
1	Chronic loss of blood (achlorhydria)	3.4 (a) to 5.0 (b)	1.9 (a) to 2.1 (b)	0.43† (mean of 13 determinations)	6 Gm. for 24 days	5.0 (a) to 11.5 (b)	2.1 (a) to 4.2 (b)	0.41† (mean of 16 determinations)	8.2
2	Chronic loss of blood (achlorhydria)	5.9 (a) to 5.0 (b)	3.0 (a) to 2.3 (b)	0.38† (mean of 18 determinations)	6 Gm. for 40 days	5.0 (a) to 11.7 (b)	2.3 (a) to 5.0 (b)	0.42† (mean of 68 determinations)	4.0
3	Chronic loss of blood (carcinoma of stomach)	5.1 (a) to 5.0 (b)	2.1 (a) to 2.2 (b)	0.42† (mean of 3 determinations)	6 Gm. for 13 days	5.0 (a) to 7.8 (b)	2.2 (a) to 3.2 (b)	0.48† (mean of 20 determinations)	8.0
4	Pernicious†	9.4 (a) to 11.2 (b)	2.6 (a) to 2.8 (b)	0.44† (mean of 9 determinations)	6 Gm. for 21 days‡	11.2 (a) to 14.0#(b)	2.8 (a) to 2.9 (b)	0.47† (mean of 40 determinations)	No response
5	Pernicious¶	5.6 (a) to 9.3 (b)	1.3 (a) to 2.1 (b)	0.48† (mean of 9 determinations)	6 Gm. for 21 days	9.3 (a) to 12.9#(b)	2.2 (a) to 2.9 (b)	0.56† (mean of 30 determinations)	No response

* Based on an average of at least two determinations. Variation between duplicates not greater than 0.04 mg. Individual variation from 0.40 to 0.54 mg. per hundred cubic centimeters of plasma.
 (a) Initial value for period.
 (b) Final value for period.

† Variations occurred in daily iron values but within limits of experimental error.

‡ Slight reticulocyte (4 per cent) response to a weakly potent liver preparation prior to this investigation.

¶ Liver therapy discontinued seven days prior to institution of iron therapy.

Increase not to be attributed to iron. (Delayed response to liver.)

* Previous adequate response (19 per cent) to liver therapy, which was discontinued prior to institution of iron therapy.

level of the plasma iron. In addition, daily determinations of iron were made on the blood plasma of this subject for twenty-one days following the single dose of ferric ammonium citrate. No change occurred in the level of iron. The subject then took 6 Gm. of ferric ammonium citrate daily, and the level of the blood plasma iron was followed for three days, without any significant change being encountered. Five grams of powdered ferrous carbonate was then substituted for the ferric ammonium citrate, and the level of the iron was followed for twenty-one days. It fluctuated between 0.42 and 0.52 mg. per hundred millimeters of plasma and averaged 0.46 mg. Since the average of the control period was 0.39 mg. and normal variations of 0.2 have been encountered, it seems reasonable to conclude that prolonged administration of iron did not result in an increase of the plasma iron.

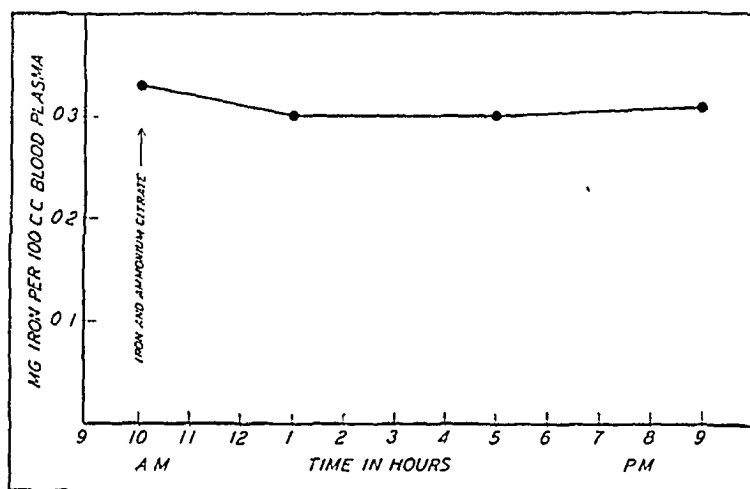


Chart 1.—The negative effect of the oral administration of 6 Gm. of iron and ammonium citrate on the iron content of the blood plasma of a normal person.

Three patients with hypochromic anemia due mainly to chronic loss of blood were studied. The results are shown in the table. Gastric achlorhydria was present in each of the three cases; prolonged dietary deficiency had existed in case 2, and carcinoma of the stomach was present in case 3. These various factors contributed to the degree of the anemia. A control period of from three to eight days was established during which time complete hematologic studies and determinations of iron were made, and the same observations were conducted daily throughout the period of treatment. The table shows that there was a prompt response of the bone marrow to the iron as indicated by the reticulocyte response and the lessening of the anemia. In cases 1 and 2 the hemoglobin increased by about 6 Gm. in four weeks. In case 3 the period of observation comprised only thirteen days, but here also a definite response occurred. In each case, however, the level of iron in the plasma remained remarkably constant during the entire period.

The results of the observations made on the two patients with pernicious anemia were similar to those on the patients with hypochromic anemia. The observations were made soon after a satisfactory reticulocyte response to liver therapy. The liver therapy was discontinued a few days prior to the control periods of seven and five days, respectively, for each case. At the conclusion of these control periods, the patients were given daily 6 Gm. of ferric ammonium citrate, and hematologic observations together with determinations of the level of iron in the blood plasma were made daily for twenty-one days. The slight increase in red cells and hemoglobin may be interpreted as due to the previous liver therapy. There was, as is shown in the table, no corresponding increase in the amount of plasma iron.

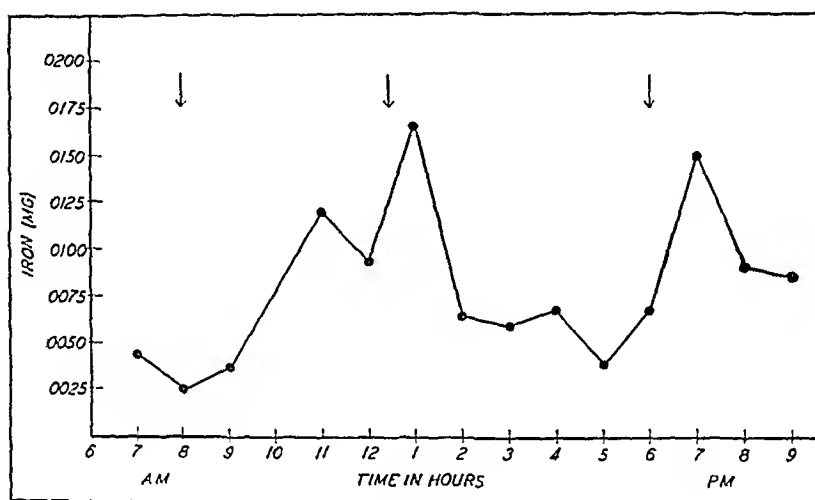


Chart 2.—The hourly excretion of iron in the urine of a normal person. The food intake is designated by arrows.

Excretion of Iron in the Urine.—The urine of two normal persons not given iron showed the average hourly excretion of iron to be 0.0026 and 0.0066 mg., respectively. The amount varied between 0 and 0.0133 mg. per hour for one person and between 0.0025 and 0.0170 mg. for the other. In every observation made on these subjects slight increases in the output of iron occurred before or after the ingestion of food. Chart 2 records a typical curve for one of these subjects. For purposes of comparison, chart 3 is presented to show the urinary excretion of iron in the same person when food was omitted. A conceivable explanation of the differences between the two curves is that slightly more iron was released to the urine owing to the secretion into the stomach of hydrochloric acid following ingestion of food. In the presence of this acid the absorption of iron was probably increased.

Since Mettier and Minot² previously reported the enhanced effect of iron administered in acid mediums, the foregoing observation suggested an investigation of the effect of administering iron in an acid medium on the urinary excretion of the substance. Hourly specimens of urine were obtained from 6 a. m. to 11 p. m. No food was taken

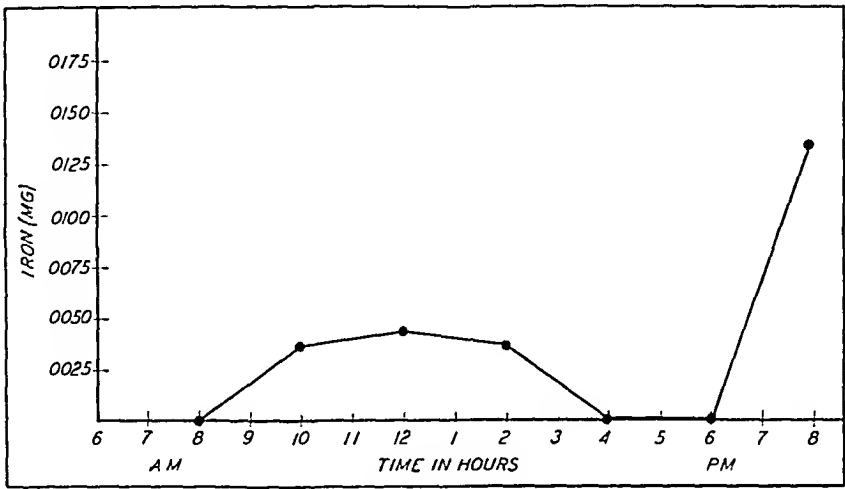


Chart 3.—The excretion of iron in the urine of a fasting normal person.

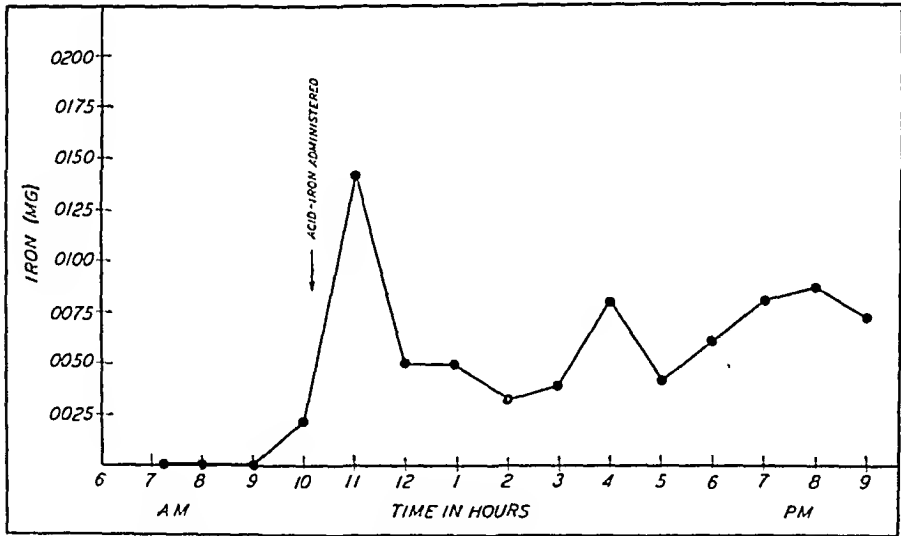


Chart 4.—The effect of the administration of iron in an acid medium on the hourly excretion of iron in the urine of a fasting normal person.

from 6 p. m. on the day preceding the experiment until shortly after 9 p. m. on the day iron was administered. Six grams of ferric ammonium citrate in aqueous solution was added to a beefsteak digestion

2. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastrointestinal Contents in Certain Cases of Anemia, *Am. J. M. Sc.* **181**:25, 1931.

mixture, prepared as described by Mettier and Minot. The reaction of the mixture was p_H 3. The material was introduced into the stomach by tube at 9:50 a. m. The curve given in chart 4 represents the hourly excretion of iron in the urine under these conditions. The maximum excretion of iron occurred at 11 a. m., or fifty minutes after the introduction of iron and food with an acid reaction. Although greater variations than indicated in chart 4 have been encountered in untreated normal persons, the finding takes on significance when compared with the hourly excretion of iron in the urine of the same person in the absence of food, and after iron therapy as indicated in chart 3.

The excretion of iron in the urine of the patients with hypochromic anemia and pernicious anemia under iron therapy did not vary markedly from that found in normal persons given no iron. The total elimination of iron in the urine of the normal persons was found to vary between 0.06 and 0.1 mg. per twenty-four hours; in that of the three patients with hypochromic anemia under iron therapy, it fluctuated between 0.02 and 0.05 mg. per twenty-four hours, and in that of the two persons with pernicious anemia, it fluctuated between 0.037 and 0.59 mg.

COMMENT

Studies of the iron content of whole blood and blood serum are recorded in the literature, but little definite information has been available concerning the amount of iron in the blood plasma of man. Riecker³ studied the iron content of serum and gives as an average normal figure 1 mg. per hundred millimeters of blood. McIntosh⁴ recently established a value of from 0.5 to 1 mg. per hundred millimeters of blood for what he calls the "non-protein iron of the blood." Changes in the values of whole blood iron indicate essentially alteration in the hemoglobin content of the blood, and do not reflect changes in the small amount of extracellular iron in the plasma. It is of interest to note that McIntosh ascribed the greater part of his "nonprotein" iron to the cell, in loose combination with hemoglobin. It has been shown that a quantitative relationship exists between the absorbed iron and the increase in hemoglobin.¹ To the blood plasma has been ascribed the function of transportation of the iron. Such a function does not seem to predicate an increase in the amount of iron in the plasma. In contradistinction to Riecker, our daily study on the plasma iron of patients with hypochromic anemia passing through a remission due to iron therapy showed no increase in the amount of iron. Nor do the

3. Riecker, H. H.: Iron Metabolism in Pernicious and in Secondary Anemia, *Arch. Int. Med.* 46:458 (Sept.) 1930.

4. McIntosh, J. F.: The Nonprotein Iron of the Blood, *J. Clin. Investigation* 12:967, 1933.

data show any increase in the amount of plasma iron with an increase in the level of hemoglobin. This sharply differentiates the observations of this investigation from the findings of McIntosh with respect to "nonprotein" iron. Although only three cases of hypochromic anemia were studied, the observations were controlled, and from twenty to seventy determinations of plasma iron were made in each case. The evidence indicates that the level of the plasma iron during the control period did not vary essentially from that found for normal persons. Prolonged and effective iron therapy did not materially affect the level of the iron in the blood plasma. Coincident increases in the total amount of blood iron, as evidenced by considerable increase in the level of hemoglobin, failed to produce a parallel increase in the level of plasma iron. On the basis of this evidence, one must conclude that the deficiency of iron in hypochromic anemia is not manifest in the blood plasma. This finding bears a close parallelism to what occurs so often in depletion of calcium. Decalcification of bone may progress to an alarming extent without decrease in the level of the serum calcium. There seems to exist a similar state of affairs in the case of plasma iron. The constancy of the plasma iron level in the patients studied was remarkable. In all probability the increase in hemoglobin during remission accounts for almost all of the iron effectively utilized by the organism.¹

The investigations on the iron content of the urine differ from previous comparative studies in that shorter intervals of time have been used. This method of investigation was adopted since evidence has been gradually accumulating which tends to show that the absorption of iron may be influenced significantly by the degree of acidity of the gastrointestinal tract.² The changes caused by ingestion of food or by changes in the acidity of the upper part of the gastro-intestinal tract are assuredly better studied by determining the excretion of iron in the urine from hour to hour than at longer intervals. The amount of iron found in the urine of normal persons and of persons with anemia was somewhat lower than that reported by Riecker³ but in close agreement with the figures given by Henriques and Roland,⁴ and more recently by Bassett.⁶ In Bassett's study the analyses were made by an electrometric method.

Examination of the data obtained seems to show a somewhat greater excretion of iron at the time food was ingested and following the administration of iron in an acid medium. It must be remembered, however, that in the study of the effect of acid the persons studied were in

5. Henriques, V., and Roland, H.: *Zur Frage des Eisenstoffwechsels*. Biochem. Ztschr. **201**:479, 1928.

6. Bassett, S. H.: Personal communication to the authors.

normal health with respect to red blood cells and hemoglobin, and presumably had a satisfactory iron balance, and that in this investigation the iron was administered to patients by the oral route. Our results are in close agreement with those of Henriques and Roland, in that these authors found no characteristic changes in the output of iron in the urine of patients with "secondary" anemia. No attempt was made to study the excretion of iron administered parenterally. It is necessary in considering the results obtained in the two cases of pernicious anemia to bear in mind that the patients had already responded to liver therapy.

The data obtained from this investigation seem to warrant the conclusions.

CONCLUSIONS

1. The iron content of the blood plasma of normal persons varies between 0.4 and 0.7 mg. per hundred cubic centimeters, while that of the urine ranges from 0.03 to 0.8 mg. per twenty-four hours.

2. The iron content of the blood plasma and urine of three patients with hypochromic anemia due mainly to chronic loss of blood and of two patients with pernicious anemia soon after remission had been inaugurated was found to vary within normal limits. The oral administration of ferric ammonium citrate to these patients and to normal persons caused no definite increase in the iron content of the blood plasma or of the urine. However, in the normal person studied there was perhaps a slight increase in the urinary excretion of iron following the oral administration of this substance in an acid-buffered medium.

Miss Eleanor R. Shea, A.B., and Miss Marion Duane assisted in the technical work.

CONGESTIVE HEART FAILURE

XVIII. CLINICAL TYPES OF NOCTURNAL DYSPNEA

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The dyspnea of cardiac disease is a complex symptom occurring under a variety of circumstances and producing a multiplicity of clinical syndromes. Except for the dyspnea produced by exertion one rarely sees the various types in "pure" form because the same patient is likely to have at the same time several different kinds of dyspnea, and as the disease progresses new types develop while the old ones do not subside.

Elsewhere we have published studies in which attempts were made to achieve a more exact understanding of the pathogenesis of orthopnea¹ and of the dyspnea produced by exertion.² In this and in succeeding papers similar efforts will be directed toward an elucidation of nocturnal dyspnea. The literature on this subject is voluminous and is complicated by the fact that there is no general agreement on nomenclature. Because of this confusion in terms we prefer to use in the following review the phrase "nocturnal dyspnea," and by this term we designate the types of respiratory distress that are likely to be especially frequent and severe at night.

THEORIES REGARDING THE PATHOGENESIS OF DYSPNEA

Although many different hypotheses have been advanced as to the pathogenesis of nocturnal dyspnea, most of them are variants or combinations of a few main theories.

Back Pressure.—This hypothesis seems to have been the first of the various theories to receive serious support of an experimental nature. William H. Welch,³ in whose contribution references to the earlier literature may be found, showed in 1878 that edema of the lungs could be produced in rabbits by ligation of the descending aorta. the branches

From the Department of Medicine, Vanderbilt University.

1. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: J. Clin. Investigation **11**:133, 1932.

2. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Arch. Int. Med. **50**:690 (Nov.) 1932.

3. Welch, W. H.: Virchows Arch. f. path. Anat. **72**:375, 1878.

of the aortic arch and of most of the pulmonary veins. As a result of his experiments he concluded that pulmonary edema in man was to be regarded as secondary to a difference in the amount of blood pumped by the two ventricles, i. e., as due to back pressure from a dilated left ventricle which failed to empty itself sufficiently. In 1885, Sahli⁴ made similar observations on dogs and was unable to produce pulmonary edema regularly. He concluded that there were other factors in addition to the mechanical ones. Forty years later, Kraus⁵ found that pulmonary edema occurred in animals only when both ventricles were working energetically; often when the left ventricle was working poorly there was no pulmonary edema.

The findings of Eppinger, von Papp and Schwarz⁶ were in general agreement with the back pressure hypothesis. These authors concluded as the result of their extensive study that two factors played a rôle in the production of the paroxysms of nocturnal dyspnea: diminished reserve power of the left ventricle and increased venous return to the heart due to peripheral vasodilatation. The result of these two factors operating simultaneously was considered to be an acute congestion of the lungs. This in turn caused the dyspnea, not by producing alterations in the composition of the blood, but by reflex stimulation of breathing. The authors did not demonstrate the existence of such reflexes but assumed them to be present and effective.

The same investigators were interested in the question as to why in many patients the attacks occurred so soon after the onset of sleep. They pointed out that in some patients dreams seemed to be the precipitating factor, but they did not believe that dreams were responsible in all instances. They found that the consumption of oxygen reached its lowest level within the first two hours after the onset of sleep and quoted the observations of Katsch and Pansdorf,⁷ who found that the same was true of the blood pressure. The brain volume and pulsations, measured by plethysmographic methods on subjects with defects in the skull, were greatest at the same time. These phenomena were interpreted as indicating a decrease in the activity of the sympathetic nervous system with a relative preponderance of the parasympathetic during sleep and especially during the first two hours of sleep. As a result a decrease in the tonus of the muscle of the heart was assumed to occur at the same time as an increase in venous return, and hence in cardiac

4. Sahli, H.: *Arch. f. exper. Path. u. Pharmacol.* **19**:433, 1885.

5. Kraus, quoted by Luisada, A.: *Arch. f. exper. Path. u. Pharmacol.* **32**: 889, 1928.

6. Eppinger, H.; von Papp, L., and Schwarz, H.: *Ueber das Asthma cardiale*, Berlin, Julius Springer, 1924.

7. Katsch, G., and Pansdorf, H.: *München. med. Wchnschr.* **69**:1715, 1922.

output, because of peripheral vasodilatation. The consequence was pulmonary congestion and an attack of cardiac asthma, which, if severe enough, led to pulmonary edema.

The theory of Eppinger and his co-workers has been a subject of some controversy. Some writers appear to have accepted it; others have not. Thus Lauter⁸ and Kroetz⁹ reported low cardiac outputs in persons with cardiac dyspnea. There is considerable doubt as to the validity of most of the present respiratory methods for determining cardiac output in persons with congested lungs, and consequently this argument cannot be regarded as settled.

Insufficient Aeration.—Traube, the great German clinician, believed that paroxysmal dyspnea (as well as other forms of cardiac dyspnea) was due to congestion of the lungs, which caused the capillaries to encroach on the air spaces (*Lungenschwellung*) thereby interfering with the ventilation of the lungs and causing defective aeration of the blood.¹⁰ This theory was modified by von Basch,¹¹ who thought that the decreased aeration was due to rigidity of the lungs (*Lungenstarre*) consequent on pulmonary congestion. However, Kraus¹² demonstrated not only that the ventilation was actually increased, but also that the alveolar carbon dioxide pressure was lower than normal in persons with cardiac failure. Hence, diminished ventilation of the lungs could not be the cause of the dyspnea.

Siebeck,¹³ in 1912, demonstrated that the vital capacity was diminished and concluded that *Lungenstarre* did occur, but he found no alteration in the residual air and hence believed that *Lungenschwellung* did not take place to a significant degree. He thought that the dyspnea was caused by the rigidity of the pulmonary tissues, which caused uneven aeration with consequent increase in the carbon dioxide pressure of the arterial blood and respiratory stimulation. Porges,¹⁴ on the other hand, confirmed Kraus' observation of abnormally low alveolar carbon dioxide pressure in persons with cardiac dyspnea. He believed that this was due to acidosis, which in turn was caused by inadequate oxygenation of the blood. Straub and Meier¹⁵ found acidosis in some but not in all the patients they studied and concluded that cardiac dyspnea was due to a carbon dioxide acidosis.

8. Lauter, S.: München. med. Wchnschr. **77**:593, 1930.

9. Kroetz, C.: Deutsches Arch. f. klin. Med. **164**:257, 1930

10. Traube, quoted by Eppinger,⁶ p. 11.

11. von Basch, quoted by Eppinger,⁶ p. 11.

12. Kraus. quoted by Eppinger,⁶ p. 13.

13. Siebeck, R.: Deutsches Arch. f. klin. Med. **107**:252, 1912.

14. Porges, O., and Marconi, E.: Wien. klin. Wchnschr. **23**:454, 1910.

15. Straub, H., and Meier, K.: Deutsches Arch. f. klin. Med. **125**:477, 1918.

All these theories of diminished aeration of the arterial blood as the cause of cardiac dyspnea have been discredited in recent years by the work of Eppinger, von Papp and Schwarz,⁶ Peters and Barr,¹⁶ Eppinger, Kisch and Schwarz,¹⁷ Fraser, Harris, Hilton and Linder,¹⁸ Cullen, Harrison, Calhoun, Wilkins and Tims,^{19a} and Calhoun, Cullen, Harrison, Wilkins and Tims,^{19b} to mention only a few of the authors who have applied modern methods to the problem. Their studies seem to be in general agreement in indicating that increased hydrogen ion concentration of the arterial blood is an exceptional finding in persons with cardiac dyspnea and occurs only in moribund patients or in patients with extreme degrees of pulmonary disease. In some instances the patients in the latter group may have carbon dioxide tensions of 60 or even 70 mm. of mercury, but such cases are rare, and usually the patients do not have paroxysmal dyspnea unless they also have bronchial asthma. Alkalosis, usually of mild degree, is on the other hand a common finding in patients with cardiac dyspnea (Fraser, Cullen, Calhoun and their co-workers).

Diminished Cardiac Output.—Most English and American investigators have concluded that the various forms of cardiac dyspnea are due to an accumulation of acid metabolites in the respiratory center dependent on a diminished cerebral flow of blood due to a decrease in the cardiac output. That this hypothesis is not correct was demonstrated in previous studies in the present series¹⁹ in which it was shown that not only the arterial blood but blood obtained from the internal jugular veins of patients with dyspnea (nocturnal or produced by exertion) failed to show any of the postulated alterations in hydrogen ion concentration, carbon dioxide or oxygen content.

Nervous Cause.—Being dissatisfied with chemical theories of paroxysmal dyspnea, some authors have believed the syndrome to have its genesis in the nervous system. Hoffmann²⁰ went so far as to assume that paroxysmal dyspnea was a neurosis of the cardiac nerves. Brunn²¹ believed the symptom to be due to a disturbance in water regulation leading to a passage of fluid from the tissues into the blood stream during the night in these patients, all of whom he believed to

16. Peters, J. P., and Barr, D. P.: J. Biol. Chem. **45**:537, 1921.

17. Eppinger, H.; Kisch, F., and Schwarz, H.: Das Versagen des Kreislaufes. Berlin, Julius Springer, 1927.

18. Fraser, F. R.; Harris, C. F.; Hilton, R., and Linder, G. C.: Quart. J. Med. **22**:1, 1928.

19. (a) Cullen, G. E.; Harrison, T. R.; Calhoun, J. A.; Wilkins, W. E., and Tims, M. M.: J. Clin. Investigation **10**:807, 1931. (b) Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. E., and Tims, M. M.: *ibid.* **10**:833, 1931.

20. Hoffmann, F. A., quoted by Eppinger,⁶ p. 9.

21. Brunn, F.: Zentralbl. f. inn. Med. **49**:873, 1928.

have latent edema. This hydremic plethora was thought to be responsible for an increase in the degree of pulmonary congestion and for the consequent paroxysmal dyspnea. As evidence he cited the fact that diuretics may prevent attacks of paroxysmal dyspnea, and, further, that the attacks are often followed by the passage of large amounts of pale urine. The same mechanism was responsible, he believed, for the well known nocturia of cardiac failure. The beneficial action of morphine is, according to Brunn, to be ascribed to its action in holding the water in the tissues (Moliter and Pick²²). In another article²³ Brunn showed that pituitary medication also tended to make the tissues retain water, and to this action, as well as to its effect on the central nervous system, he ascribed the beneficial effects of this drug in cases of paroxysmal cardiac dyspnea.

Gollwitzer-Meier²⁴ also believed that the seizures were due to nocturnal passage of water from the tissues into the blood stream. This led to pulmonary congestion (in persons with a strained left ventricle) which resulted in a decrease in the residual air which in turn caused reflex stimulation of breathing. This reflex was assumed but not demonstrated.

Brunn's hypothesis is attractive because it accounts for the fact that diuretic drugs, even if followed by only slight diuresis, may have a pronounced effect in preventing the attacks of dyspnea. However, the passage of fluid into the blood stream has not yet been demonstrated. If it did occur in significant amounts one would expect the hemoglobin concentration of the blood of such patients to be lower in the morning than in the evening. Actually, the reverse is true, as will be shown in the succeeding study in this series. The oxygen capacity is usually higher in the morning than in the evening, and this fact seems to us to constitute rather strong evidence against the validity of the "water shift" hypothesis.

Danzer²⁵ believed that an increase in the spinal fluid pressure during sleep might be a factor in the production of the attacks of dyspnea but offered no convincing evidence for his theory.

A number of authors believe that paroxysmal dyspnea is a reflex disturbance. The opinion of Eppinger, von Papp and Schwarz and of Gollwitzer-Meier, that reflexes from the lungs are responsible, has already been mentioned. Hess²⁶ believed the dyspnea to be due to a

22. Moliter, H., and Pick, E.: *Arch. f. exper. Path. u. Pharmacol.* **107**:185, 1925.

23. Brunn, F.: *Ztschr. f. d. ges. exper. Med.* **25**:176, 1921.

24. Gollwitzer-Meier, K.: *Klin. Wchnschr.* **10**:341, 1931.

25. Danzer, C. S.: *Ann. Int. Med.* **2**:239, 1928.

26. Hess, L.: *Wien. Arch. f. inn. Med.* **12**:477, 1926.

reflex effect on the pulmonary arteries from a myelomalacic heart. He supported his opinion by reports of pathologic conditions occurring in hearts, but not by conclusive experiments. Luisada²⁷ studied pulmonary edema produced in rabbits by the administration of epinephrine. He showed that drugs which stimulate the respiratory center increase the sensibility of these animals to pulmonary edema produced in this way, and that drugs which depress the brain have the opposite result. He also found that cutting the spinal cord in the cervical region prevented the development of pulmonary edema following the administration of epinephrine, and concluded that the effect of epinephrine was due not so much to the rise in blood pressure as to a reflex from the heart or aorta acting on a (hypothetic) center assumed to regulate the permeability of the pulmonary capillaries. Luisada's contribution contains an excellent review of the literature on the mechanism of the production of pulmonary edema.

Wassermann²⁸ described the cases of patients with angina pectoris and paroxysmal dyspnea, which he believed were due to a reflex from the root of the aorta, because relief was obtained by cutting the depressor nerves. Later,²⁹ he reported a rise in blood pressure and an increase in pulse rate occurring just before the attack of dyspnea. These signs led him to believe that the cause of the attacks was reflex stimulation of the central nervous system. He sought to produce an antagonistic reflex by pressure on the carotid sinus, a measure which was found beneficial in some instances. Wassermann concluded that paroxysmal dyspnea was a reflex from the aorta and that pulmonary edema was also due to a reflex of similar origin, causing narrowing of the pulmonary vessels.

Cheyne-Stokes Respiration.—Sir James Mackenzie³⁰ stated that the paroxysms of nocturnal dyspnea were to be attributed to Cheyne-Stokes respiration but offered no explanation for the cause of the latter phenomenon.

As a result of this summary of some of the more important contributions in the literature it may be stated that there seems to be general agreement that nocturnal dyspnea is in some way related to disturbed function of the cardiovascular system, but that the greatest diversity of opinion exists concerning the exact pathogenesis of this syndrome. We believed that any systematic investigation of the subject must begin with a clinical study. For the past four years we have carefully kept

27. Luisada, A.: Arch. f. exper. Path. u. Pharmacol. **32**:889, 1928.

28. Wassermann, S.: Wien. klin. Wchnschr. **37**:889, 1924.

29. Wassermann, S.: Wien. klin. Wchnschr. **40**:517, 1927.

30. Mackenzie, James: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925, p. 33.

records of patients' statements in regard to their dyspnea. The earlier records are of relatively little value because we did not at first know what questions to ask. However, our last thirty patients with nocturnal dyspnea have been exhaustively questioned, and the data of the present paper were obtained from their records. These data are based on the patients' statements in regard to their respiratory distress and, being subjective, are open to all the sources of error inherent in such studies. However, before we could make investigations by more exact methods it was necessary to have a starting point. The subjective aspects of the syndrome seemed to be a logical point of departure for the objective investigations to be reported later.

CLINICAL OBSERVATIONS

Of the thirty patients, three were observed in private practice and the remainder in the clinic for cardiac diseases and in the medical wards of the Vanderbilt University Hospital. Thirteen of the patients were ambulatory, and seventeen were observed while being treated in the hospital. The data in regard to the latter persons are somewhat more full because of the greater opportunity for clinical observations.

Race and Sex.—The series consisted of eleven white men, four white women, eight Negro men and seven Negro women, a total of fifteen white and fifteen Negro patients.

Age.—The oldest patient in the series was 68 years of age; the youngest was 23. The distribution by decades was as follows: between the ages of 20 and 30, three cases; between 30 and 40, two cases; between 40 and 50, twelve cases; between 50 and 60, seven cases, and between 60 and 70, six cases.

Chief Etiologic Factors.—In a number of patients more than one underlying cause of heart disease was present, and such persons have been classified according to which of these seemed to be most important. Accordingly, hypertension was considered as the chief etiologic disorder in fourteen cases; syphilitic aortic insufficiency in six; arteriosclerosis in five, and a rheumatic condition in two. The two last mentioned had mitral stenosis, and one of them had aortic insufficiency as well. In three patients none of the common causes of heart disease was present, and the conditions in these patients were classified under the term "cardiac hypertrophy, cause unknown." Three patients, in addition to having definite organic cardiac disease, presented all the signs and symptoms of cardiac neurosis. All of these were white female patients. One of them had the only case of uncomplicated mitral stenosis in the series. Her seizures of dyspnea occurred only in association with excitement, emotion, unpleasant dreams and "nervousness," and it seems probable that they were related to her cardiac neurosis rather

than to her organic cardiac disease. If this patient is excluded from the series, there remains no case of uncomplicated mitral stenosis in the group.

A number of authors have referred to paroxysmal dyspnea as a symptom of syphilitic aortitis in its earliest stage. There was no patient with that condition in this series, every patient with syphilitic aortitis having associated aortic insufficiency, hypertension or arteriosclerosis as a cause of dyspnea. In this clinic many cases of syphilitic aortitis are observed, and our experience indicates that this disorder in its uncomplicated form practically never causes paroxysmal dyspnea.

Eight patients in the series had angina pectoris, but only four of them had ever had the pain and the dyspnea simultaneously, and even these subjects had had many attacks of dyspnea without pain, and vice versa. It is therefore unlikely that any causal relationship exists between these two symptoms.

Objective Findings.—Aside from the characteristic clinical phenomena associated with the underlying disease, the patients with nocturnal dyspnea have regularly shown two signs, i. e., demonstrable cardiac enlargement and diminution in vital capacity. The majority of the patients had obviously enlarged hearts, but in a few obese patients, in whom the physical signs left one in doubt, teleroentgenograms have demonstrated an abnormally wide cardiac shadow. The vital capacity was not measured in three subjects, but the remaining twenty-seven exhibited a diminution of this function when compared to the normal standards of Peabody and Wentworth.³¹ Gallop rhythm was noted in eight of the thirty subjects. Four patients had auricular fibrillation, and twenty exhibited premature beats. Cheyne-Stokes respiration was present in one half of the cases and will be discussed later.

Duration of Symptoms.—Every patient gave a history of more or less respiratory distress on muscular effort, but the duration of this symptom was variable. The longest duration was ten years, the shortest, one month, and the average, three and one-tenth years. Each of the patients had nocturnal dyspnea which varied in duration from five years to one month, the average being two and one-tenth years.

Edema had been present at one time or another in twenty-three of the thirty cases. The average period after edema was first noted was approximately one and one-half years. As a rule it was a late symptom, and in only three cases did edema develop prior to the onset of nocturnal dyspnea.

31. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration: V. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. 20:443 (Sept.) 1917.

Predisposing and Precipitating Factors.—From what has been stated it appears that paroxysmal dyspnea is associated with disorders that cause a strain on the left side of the heart and more particularly with those that cause an initial strain on the left ventricle. In addition, however, there are a number of conditions which appear to bring on the seizures, and concerning these our patients have been questioned in considerable detail.

Position of the Body: Twenty-seven of the thirty patients stated that they were more short of breath in the recumbent than in the sitting posture. The remaining three patients who did not have orthopnea had paroxysmal dyspnea for two months or less and were the earliest subjects of the series. Three patients stated that they were more comfortable standing than sitting, but the majority agreed that the most favorable position was sitting on the side of the bed with their feet resting in a chair.

Blumgart and Ernstene pointed out the fact that the position of the patient's head may affect his dyspnea. Eleven of our patients preferred to have the head flexed.

Cough: This was an extremely frequent symptom. Seven patients said that their attacks were invariably precipitated by coughing, and that they never had attacks except following coughing. Sixteen additional persons stated that some of their attacks were precipitated by coughing but that they also had seizures which did not follow coughing. Seven patients stated that their attacks bore no relation to coughing. Expectoration of sputum tended to relieve the attack in fifteen of the twenty-three patients who had noted cough as a factor in the production of their seizures.

Activity: An important predisposing factor in many patients was the amount of activity indulged in during the day. Twenty-one patients had noted that they were more likely to suffer from nocturnal dyspnea following a day of activity than they were after they had been relatively quiet during the day. On the other hand, nine patients insisted that they were just as likely to have seizures after a day of rest as after a day of moderate activity.

Abdominal Distention: Seventeen patients observed that they were especially likely to be dyspneic when they suffered from distention, and these patients stated that either belching or the passing of flatus often relieved their seizures.

Size of the Preceding Meal: Twelve patients noted that a large evening meal appeared to be a predisposing cause of their attacks, which could be prevented or ameliorated by omission of the evening meal.

Bowel Movements: Twelve patients had noticed that they were more apt to have dyspneic seizures when they were constipated, and

that their breathing seemed easier following bowel movements. In these persons the dyspnea was not simply related to straining at stool; they all stated that their dyspnea began when they first noticed the desire for a bowel movement, tended to become worse the longer the defecation was postponed and disappeared within a short time following emptying of the rectum.

Hunger: One patient stated that nearly all his attacks occurred when he was hungry. He frequently asked for milk and a cracker and usually seemed to have less dyspnea following ingestion of that food. (Determinations of blood sugar made during his seizures revealed no hypoglycemia.) Seven other patients reported that they were likely to have seizures during hunger, and that the eating of a small amount of food often made them feel better, whereas the eating of large meals made the attacks worse.

Dreams: Several authors have pointed out that unpleasant dreams tend to cause seizures of paroxysmal dyspnea in certain patients, and this appeared to be the case in eight of our thirty cases. Three of these eight patients were white women who, in addition to having organic cardiac disease, were definitely psychoneurotic. However, the other five persons displayed no undue anxiety and had none of the usual signs of neurosis. Two of the patients had no nocturnal seizures at all except following nightmares or unpleasant dreams, whereas in the remaining six dreams were only one of several precipitating factors.

Temperature: For a number of years we have noticed that at the onset of unusually hot weather patients coming to the clinic for cardiac diseases are likely to complain of nocturnal dyspnea. In the present series, eight persons stated that heat was an important predisposing or precipitating factor in their attacks, and one of them stated that the warmth of the bed clothes appeared to cause seizures. The first attack in two patients occurred during very hot weather, and both of them have continued to have seizures whenever the room in which they sleep is unusually warm.

Urination: Seven patients complained of noticing dyspnea when they wanted to empty the bladder, and in two of them we had occasion to make objective studies concerning the breathing at such periods. The results, which will be published in a subsequent article, indicated clearly that dyspnea was aggravated by the desire to urinate and was relieved immediately following micturition.

Time of Onset of the Attacks.—The patients were questioned carefully in regard to the exact hour at which they noticed respiratory distress and as regards the relation of the attacks to the waking and sleeping states. Ten patients, most of whom had relatively mild dyspnea, stated that they never suffered from respiratory distress as long as they

were awake, at rest and in the upright position. They did, however, suffer from seizures during sleep. Twenty patients who had somewhat more severe dyspnea stated that they sometimes suffered from respiratory discomfort during their waking hours, even though they were at rest and in the sitting position. Of this group, one patient who had severe attacks of coughing each morning on awakening stated that the dyspnea was always worse in the morning when he coughed than in the evening, and two persons noticed no difference in the dyspnea during different parts of the day. However, the remaining seventeen subjects agreed that the dyspnea, when it occurred at all during their waking hours, was always more severe in the late afternoon—especially in the evening—than it was in the morning. They also stated that even though they remained in bed and in the same position throughout their waking period, their distress would still be worse toward the latter part of the day. Objective studies, which will be reported in the succeeding paper, were made in the patients who were in the hospital, and their statements were confirmed. It appears, therefore, that something occurs during the day which in many patients tends to produce dyspnea as night draws on. During the morning a patient may be entirely comfortable so long as he remains propped upright and at rest. At about 4 or 5 o'clock in the afternoon he is likely to notice a little discomfort, and by 8 or 9 o'clock he may have fairly severe respiratory distress. It should be noted that this type of dyspnea is nocturnal but not paroxysmal.

All of the thirty patients complained of attacks of shortness of breath which awakened them from sleep. Twenty stated that they frequently had seizures occurring immediately at the onset of sleep. Although relatively or entirely free from dyspnea on first settling themselves for the night, they would awake suddenly, just as they began to "doze off" to sleep, with a seizure of respiratory distress. Following a few minutes or seconds of discomfort they would become relieved and would again become somnolent only to experience another attack just as they passed into the sleeping state. Of these twenty patients, eight had no attacks except those of the nature described, whereas twelve also complained of seizures which awakened them from sound sleep after they had been sleeping for one or more hours. The latter attacks were often described as being of longer duration and more severe.

It is of interest to note that Cheyne-Stokes respiration was found in fifteen of the twenty patients who had seizures of dyspnea occurring at the onset of sleep. In the remaining five who had dyspnea of this type, periodic breathing was not observed, but these were ambulatory and were not seen during attacks. It is possible that these patients also might have been found to have Cheyne-Stokes breathing if they

had been observed during their seizures of dyspnea. The frequency with which patients complaining of shortness of breath of this type have exhibited Cheyne-Stokes respiration has made us wonder whether or not the subjective respiratory distress could be related in some way to their periodic breathing. Objective observations concerning this question will be presented in a later contribution.

Ten patients in the series of thirty stated that their seizures never came at the onset of sleep but always appeared after they had slept soundly for one hour or more. None of these patients had been found to have Cheyne-Stokes respiration. As has been stated, there were twelve persons who had seizures both at the onset of sleep and later on after sleep had lasted for an hour or more.

Attacks of acute pulmonary edema have been observed in six of the thirty patients. All these attacks have appeared after the subject had been asleep for some time, and no attack has occurred at the onset of sleep. Furthermore, no patient whose dyspneic seizures were limited in their occurrence to the onset of sleep has had an attack of acute pulmonary edema.

It is of interest to consider the ages of the patients in respect to the type of dyspnea experienced. The average age of the eight patients who had paroxysmal dyspnea only at the onset of sleep was 55 years, the youngest being 43 and the oldest, 68. These figures are in contrast to those for the ten subjects who had attacks which awakened them from sound sleep. Their average age was 42, the range being from 23 to 54. The twelve subjects who had attacks of both types were, as might be expected, intermediate in this respect, the average age being 50 years and the range of ages from 39 to 66.

SUMMARY

A clinical study has been made of thirty patients who had cardiac disease and who suffered from attacks of nocturnal dyspnea. Most of the subjects were more than 40 years of age. The chief causes of cardiac disease in these cases were hypertension, arteriosclerosis, and syphilitic aortic insufficiency. There were only two patients with rheumatic heart disease, and of these, only one had uncomplicated mitral stenosis. The occurrence of nocturnal dyspnea is restricted almost entirely to patients with disorders which cause a strain on the left ventricle. Uncomplicated syphilitic aortitis (i. e., without aortic insufficiency, occlusion of the coronary vessels or aneurysm) practically never causes nocturnal dyspnea.

Cardiac enlargement and diminished vital capacity were constant objective findings; premature beats and gallop rhythm occurred in a large number of the patients. Only four patients in the series had auricular fibrillation.

The following factors have been found to be precipitating and predisposing causes of the attacks: (1) the position of the body in twenty-seven cases, (2) cough in twenty-three cases, (3) the amount of activity engaged in during the preceding day in twenty-one cases, (4) abdominal distention in seventeen cases, (5) large evening meals in twelve cases, (6) constipation and the desire for bowel movement in twelve cases, (7) hunger in eight cases, (8) unpleasant dreams in eight cases, (9) heat in eight cases and (10) urination in seven cases.

Analysis of the histories of the cases indicates that nocturnal dyspnea may be subdivided into several types of respiratory distress:

1. A type which is not paroxysmal but which develops gradually during the course of the day, usually appearing first in the late afternoon and reaching its maximum intensity at bedtime. For this syndrome the name "evening dyspnea" is proposed.

2. Attacks of shortness of breath appearing only at the onset of sleep and tending to prevent the patient from reaching a state of deep sleep. However, if such a patient falls into a sound sleep he is likely to remain free from attacks throughout the remainder of the night. Patients with this type of dyspnea frequently exhibit Cheyne-Stokes respiration and are unlikely to have seizures of acute pulmonary edema.

3. Attacks of dyspnea which begin after the patient has begun to sleep soundly and which are likely to cause acute edema of the lungs. Cheyne-Stokes respiration is an infrequent finding in patients with this type of dyspnea.

4. Combination forms. The same patient may have all three types of dyspnea, or any two of them.

In subsequent articles objective observations will be presented concerning these various forms of respiratory distress.

THE DIFFERENCE IN CREATINE CONCENTRATION OF THE LEFT AND RIGHT VENTRICULAR CARDIAC MUSCLES

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Although the function of creatine in muscle has not been entirely elucidated, recent studies indicate that in the form of phosphocreatine it plays a vital rôle in muscular contraction. Data on the creatine content of the heart, the body's most active muscle, should possess considerable significance. When one of us (D. P. S.) was approached with regard to collaborating on a study of the creatine content of the heart, an idea formulated during the progress of pathologic studies, namely, that the left and right ventricles were qualitatively different muscles, led to the decision to make separate determinations on the two ventricles.

The idea that the ventricles may be different originated about ten years ago, during a review of the available data on the congenital anomalies of the heart which result from defects of development of the bulbus cordis. As summarized by Keith,¹ the data disclosed that the conus of the right ventricle was embryologically different from other portions of the heart.

Anatomic evidence that the two ventricles might be different was found in the works of MacCallum,² Mall³ and others, whose careful

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The chemical data in this paper are taken from a dissertation being submitted by Charles R. Linegar to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

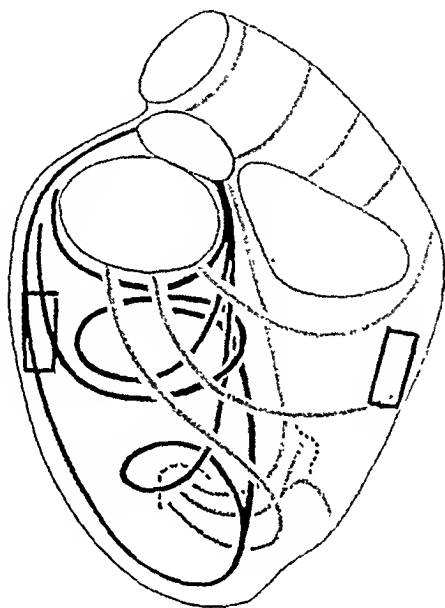
1. Keith, A.: Fate of the Bulbus Cordis in the Human Heart, *Lancet* **2**:1267, 1924.

2. MacCallum, J. B.: On the Muscular Architecture and Growth of the Ventricles of the Heart, *Johns Hopkins Hosp. Rep.* **9**:307, 1900.

3. Mall, F. P.: On the Muscular Architecture of the Ventricles of the Human Heart, *Am. J. Anat.* **11**:211, 1910-1911.

dissections revealed that the heart was not a single muscle, but was made up of overlapping and intertwining bundles, the chief of which were fairly separate and distinct for each of the two ventricles, as shown in the illustration.

Observations regarding differences between the left and right ventricles in relation to hypertrophy, dilatation, inflammations and degenerations made clinically and at autopsy suggested that these might not be due to the inequality merely in volume or quantity of the muscle of the respective ventricles, but that they could better be explained on qualitative differences between the muscles of the ventricles, differences such as are found between the various types of muscle in the same body.



Reproduction (from Mall³) showing schematically the course of the chief muscle bundles of the heart. The regions marked out are the locations at which the specimens were taken for the standard creatine determinations.

Finally, in unpublished histologic and cytologic studies it was found that in the hearts of the common laboratory animals the left ventricle contained larger amounts of glycogen and of mitochondrial substance than the right.⁴

The histologic studies revealed chemical differences between the two ventricles as pertains to glycogen and lipids. At this time the observations establish further chemical differences between the two ventricles, namely, the left ventricle has a higher concentration of creatine than the right.

The chemical studies to be recorded, therefore, in addition to furnishing data on the distribution of creatine in the muscles of the heart, also serve to demonstrate differences between the two ventricles.

4. Seecof, D. P.: Unpublished observations.

MATERIAL

The observations are based on 114 human and 9 animal hearts. The material used in correlated studies is given under the respective headings. The human hearts were obtained at autopsy from patients varying in age from birth to 83 years who died of various diseases. The animal hearts were obtained at the abattoir.

The ventricular samples for the chief analyses were taken from identical locations in each heart. These sites were chosen because they represented, as far as can be practically determined, the regions where, according to McCallum and Mall, the chief muscle bundles of the two ventricles are separate (illustration). In several instances other regions of the heart were taken to determine if the sites chosen were correct.

The samples were carefully trimmed of the epicardial fat and fibrous tissue, musculi carnae and endocardium.

The determinations on voluntary muscle were made, with few exceptions, on the pectoralis major of the same subject. For some studies, rabbit muscle was used.

METHOD

A. Actual.—The method employed in this work is a modification of that of Rose, Helmer and Chanutin.⁵

Procedure: Approximately 1 Gm. of cardiac (same procedure for voluntary and other muscle) muscle, stripped of visible fat, blood vessels, fibrous tissue, endocardium and epicardium is dropped into a previously weighed, glass-stoppered 100 cc. Erlenmeyer flask containing 20 cc. of double normal sulphuric acid. After the flasks are weighed, they are placed in the autoclave for forty-five minutes at 15 pounds' pressure. The flasks are then removed from the autoclave, twirled to break up the partially disintegrated fragments of muscle, and placed in the ice-box until the contents of the flasks are cooled to about 3 to 5 C. Now the contents of each flask are transferred to a 100 cc. volumetric flask with the aid of from 40 to 50 cc. of cooled distilled water and treated with 20 cc. of double normal sodium hydroxide which will bring the solution sufficiently close to room temperature. The reaction of the solution at this time should be faintly acid to either congo or methyl red. After the contents of each volumetric flask are diluted to volume, they are poured into a 250 cc. Erlenmeyer flask containing (exactly) 100 cc. of purified and saturated solution of trinitrophenol and mixed thoroughly. As soon as the precipitate has become flocculent, the half-saturated solution of trinitrophenol is filtered.

For the colorimetric determination, 2 cc. of 10 per cent sodium hydroxide is added to 20 cc. of this filtrate. After it is mixed, the solution is allowed to stand for ten minutes in order to develop the color completely, and a reading is made within fifteen minutes against a standard solution similarly prepared. (It is convenient to place these solutions against a white background in a porcelain pan so that the unknown solutions can be segregated with their corresponding standard solution before the readings are made.) Instead of using a curve for the colorimetric estimation, four standards were made up in half-saturated solution of trinitrophenol to contain 0.1, 0.15, 0.2 and 0.3 mg. of creatinine (of determined purity) per twenty cubic centimeters, respectively. If 1 Gm. samples are taken, these standards cover a range of from 116 to 348 mg. of creatine per hundred

5. Rose, W. C.; Helmer, O. M., and Chanutin, A.: A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissue, *J. Biol. Chem.* 75:543, 1927.

grams of cardiac muscle. For extremely low creatine values or in instances when it was impossible to obtain 1 Gm. of stripped muscle from the right ventricle, two other standard solutions were employed. These two standards contained 0.05 and 0.075 mg. per twenty cubic centimeters, respectively.

Calculation:

$$\frac{S}{R} \times S_1 \times \frac{200}{20} \times \frac{100}{W} \times \text{factor} = \text{mg. of creatine per hundred grams of muscle.}$$

S = standard setting in mm.

R = unknown reading in mm.

S₁ = strength of standard, i. e., mg. of creatinine per twenty centimeters

W = weight of specimen

Factor = 1.16

TABLE 1.—*Error of Methods in Determining Creatine Content of Muscle*

Method of Protein Precipitation	Source	Number of Experiments	Number of Samples	Range		Variation, per Cent
				Low, Mg.	High, Mg.	
Tungstic acid	Rabbit voluntary muscle	3	5	530	557	5.1
			5	518	537	3.7
			3	528	539	2.1
	Human heart muscle	3	4	180	191	6.1
			2	188	146	5.8
			2	197	202	2.5
Trinitrophenol	Human heart muscle	6	4	229	241	5.2
			4	215	226	5.1
			4	158	164	3.8
			4	266	275	3.4
			3	172	176	2.3
			3	173	176	1.7
	Human voluntary muscle	2	3	390	409	4.9
			2	384	395	2.9

B. Experimental Error.—Preliminary determinations were carried out, the tungstic acid precipitation method of Rose, Helmer and Chanutin⁵ being used. Although very satisfactory for rabbit voluntary muscle, this method did not apply so well to cardiac muscle because some of the tungstic acid filtrates were not entirely freed from a tinge of the color present in the autoclave specimens. It was found that saturation with dry trinitrophenol gave more satisfactory precipitation. Later half-saturated trinitrophenol was used because it was more expeditious. The values obtained by this modified procedure agreed closely with those of the tungstic acid method in the few comparisons made on rabbit voluntary muscle.

In order to evaluate the experimental error, several adjacent samples of muscle were analyzed simultaneously. Table 1 shows that the per cent variation with such checks on human cardiac muscle ranged from 1.7 to 5.2 per cent (average 3.5 per cent) and from 2.9 to 4.9 per cent for human voluntary muscle. In addition, samples ranging in weight from 0.4 to 3 Gm. and analyzed similarly gave figures within this range of experimental variation.

C. Recovery Experiments.—In the recovery experiments shown in table 2, creatine or creatinine in varying concentrations was added to muscle and the whole analyzed for total creatine (plus creatinine). In order to estimate the total creatinine in each sample, adjacent duplicates were analyzed and the two creatine values

averaged. Then by adding this averaged figure and the known addition, the total creatine value was obtained. The $\frac{\text{estimated value}}{\text{analytical value}}$ constituted the per cent of recovery. The per cent of recovery for this method ranged from 95.9 to 98.7 per cent on human cardiac muscle and from 94.3 to 103.7 per cent for the tungstic acid procedure. This establishes the maximum experimental error at about 5 per cent.

Further confirmation of the values in the experimental data is offered by the range of from 517 to 556 mg. creatine per hundred grams of muscle obtained for rabbit voluntary muscle, which is in close agreement with the observations of Dorner,⁶ Mellanby,⁷ Myers and Fine,⁸ Bauman,⁹ Riesser¹⁰ and Palladin and Wallenburger.¹¹

D. Samples of Different Locations.—In order to check the fact that the sites chosen for examination were correct, different portions of each ventricle, the inter-

TABLE 2.—*Recovery After Addition of Known Amounts of Creatine and Creatinine (in mg. per Gram)*

Method of Precipitation	Source	Calculated Creatine Content, Mg.	Addition as Creatine, Mg.	Total Creatine, Mg.	Creatine Found, Mg.	Per Cent Recovery	Deviation from 100%
Tungstic acid	Rabbit voluntary muscle	7.06	3.00	10.06	10.01	99.5	—0.5
		10.08	3.00	13.08	12.54	95.9	—4.1
	Human right ventricle	1.01	0.46	1.47	1.50	102.0	+2.0
Trinitrophenol	Human left ventricle	1.94	0.46	2.40	2.33	99.2	—0.8
		2.36	0.46	2.82	2.81	99.6	—0.4
		1.04	2.09	3.13	2.95	94.3	—5.7
		2.01	2.09	4.10	4.25	103.7	+3.7
	Human left ventricle	1.79	2.00	3.79	3.71	97.9	—2.1
		1.88	2.00	3.88	3.72	95.9	—4.1
		1.95	3.48	5.43	5.33	98.2	—1.8
		2.03	3.48	5.51	5.43	98.7	—1.8

ventricular septum and the muscoli carnae were examined separately. In two experiments it was found that the septum gave figures 7 per cent lower, and the right ventricle figures 23 per cent lower, than the standard specimen of the left ventricle, showing that in creatine content the septum was intermediate between the left and the right ventricles. Different regions of the same ventricle in four experiments showed differences up to 6 per cent for the left ventricle and up to

6. Dorner, G.: Zur Bildung von Kreatin und Kreatinin im Organismus, besonders der Kaninchen, *Ztschr. f. physiol. Chem.* **52**:225, 1907.

7. Mellanby, E.: Creatin and Creatinin, *J. Physiol.* **36**:447, 1908.

8. Myers, V. C., and Fine, M. S.: The Creatine Content of Muscle Under Normal Conditions: Its Relation to the Urinary Creatinine, *J. Biol. Chem.* **14**:9, 1913.

9. Bauman, L.: The Determination of Creatine in Muscle, *J. Biol. Chem.* **17**:15, 1914.

10. Riesser, O.: Weitere Beiträge zur Frage der Kreatinbildung aus Cholin und Betain, *Ztschr. f. physiol. Chem.* **90**:221, 1914.

11. Palladin, A., and Wallenburger, L.: Contribution à l'étude de la formation de la créatine dans l'organisme animal, *Compt. rend. Soc. de biol.* **78**:111, 1915.

24 per cent for the right as compared with the standard specimens of the respective ventricles. In three experiments the muscoli carnea of the left ventricle showed 31 per cent less, and the muscoli carnea of the right showed 22 per cent less, than the standard specimens of the respective ventricles.

OBSERVATIONS

A. Control Data.—I. Analysis of Dried Material: Cardiac muscle dried to constant weight at 60 C. gave from 90 to 116 per cent of the fresh weight values, and when dried at 104 C. gave from 18 to 82 per cent of the fresh weight values. Cardiac muscle, therefore, behaved similarly to other muscle in that it was not feasible to dry it before

TABLE 3.—Percentage Difference Between Left and Right Ventricles in Relation to Variation in Solid Content *

No. of Cases	Source	Range	Solid†		Ventricle				Absolute Difference, Left—Right	
			Left Ventricle, per Cent	Right Ventricle, per Cent	Left		Right		Wet, per Cent	Dry, per Cent
					Wet, Mg.	Dry, Mg.	Wet, Mg.	Dry, Mg.		
30	Human heart	Minimum	19.7	16.8	128	516	93	460	12.0	2.1
		Maximum	24.8	23.8	348	1,568	196	1,127	54.6	57.7
		Average	21.9	20.0	195	890	133	669	31.1	24.8
9	Animal heart	Minimum	20.5	19.8	245	1,075	208	941	8.6	6.0
		Maximum	24.5	23.6	379	1,745	328	1,547	21.9	19.9
		Average	22.4	21.8	308	1,385	265	1,226	14.0	11.5

* Dried to constant weight at 60 C. Dry values calculated (mg. per hundred grams of dry weight).

† The solid content of the right ventricle was higher than in the left in only one case (human): left ventricle, 22.2 per cent; right ventricle (fibrous), 23.8 per cent.

analysis. The values obtained at 60 C. were less variable, and this temperature was used for the determinations of the solid content.

Table 3 shows that the left ventricle had the higher solid content, and that the average individual difference between the left and the right ventricles in per cent of solid was higher in the human than in the animal hearts. In order to establish the difference in creatine in the two ventricles on a dry basis, the dry weight values were calculated from the fresh content by the equation: $\frac{\text{fresh weight creatine}}{\text{per cent of solid} \times 100} = \text{mg. of creatine per hundred grams of dry muscle}$. The difference in 30 human hearts, when placed on a dry basis, decreased from 31.1 to 24.8 per cent, while the decrease in 9 animal hearts was from 14 to 11.5 per cent. The per cent of difference between left and right ventricles when calculated in "dry" weight remained sufficiently high for one to assert that the final differences were due only in small part to the variations in the water content of the two ventricles.

II. Autolysis and Postmortem Factors: The preliminary analyses made on 12 human hearts kept in the refrigerator at 4 C. for periods of from two to eight days following autopsy at once indicated that the

left ventricle had a higher creatine content than the right ventricle. In this series, the average creatine value for the left ventricle was 142 mg. and for the right 94 mg., giving an average difference of 34 per cent.

In order to determine the possible rôle of postmortem factors, autolysis, etc., 9 hearts were obtained from animals immediately on slaughter at the abattoir (table 4). In each of these hearts the creatine content of the left ventricle was higher than that of the right, and for the series the differences averaged 14 per cent. Moreover, as shown in table 5, the creatine content of 5 of these hearts was not greatly altered up to nine days in the refrigerator, in spite of the slight increase in the per cent of solid due to loss of water. In this connection it may be pointed out that the experiments of Myers and Fine,¹² Hoagland and McBryde,¹³ Hammett,¹⁴ Riesser,¹⁵ and Hahn and Meyer¹⁶ showed that antiseptic or

TABLE 4.—*Creatine Content of Left and Right Ventricles in Nine Animal Hearts*

Source	Left Ventricle, Mg.	Right Ventricle, Mg.	Average Combined Left and Right, Mg.	Difference Between Left and Right	
				Mg.	Per Cent
Beef.....	370	312	341	58	15.7
	379	328	354	51	13.5
	287	253	278	29	10.1
	280	249	265	31	11.1
	245	208	227	37	15.1
	266	243	255	23	8.6
Calf.....	335	294	315	41	12.4
	270	230	250	40	14.8
Lamb.....	342	267	305	75	21.9
Average.....	308	265	287	43	14.0

aseptic autolysis has no significant effect on the total creatinine (creatine plus creatinine) content of voluntary muscle, brain, liver, kidney and blood.

12. Myers, V. C., and Fine, M. S.: The Metabolism of Creatine and Creatinine: X. The Relationship Between Creatine and Creatinine in Autolyzing Tissue, *J. Biol. Chem.* **21**:583, 1915.

13. Hoagland, R., and McBryde, C. N.: Effect of Autolysis upon Muscle Creatine, *J. Agric. Research* **6**:535, 1916.

14. Hammett, F. S.: Creatinine and Creatine in Muscle Extracts: III. Concerning the Presence of Enzymes in Muscle Tissue Which Have Creatine and Creatinine as Their Substrates, *J. Biol. Chem.* **53**:323, 1922. V. A Comparison of the Rate of Creatinine Formation from Creatine in Extracts of Brain and Muscle Tissue, *ibid.* **59**:347, 1924.

15. Riesser, O.: Beiträge zur Physiologie des Kreatins, *Ztschr. f. physiol. Chem.* **120**:189, 1922.

16. Hahn, A., and Meyer, G.: Ueber die gegenseitige Umwandlung von Kreatin und Kreatinin: IV. Die Entstehung von Kreatinin im Organismus, *Ztschr. f. Biol.* **78**:91, 1923.

However, 2 human hearts kept in the refrigerator for three and four days following autopsy showed a marked decrease in creatine content. The three day samples showed a decrease of 8 per cent for the left ventricle and of 11 per cent for the right, while the four day samples showed a decrease of 27 per cent for the left and of 28 per cent for the right. In 3 human hearts left for three days in unsterilized containers

TABLE 5.—*Effect of Autolysis on Creatine Values (Average Figures)*

No. of Hearts	Source	Days	Per Cent Solid		Ventricle		Absolute Difference, Left-Right, per Cent
			Left Ventricle, per Cent	Right Ventricle, per Cent	Left Wet, Mg.	Right Wet, Mg.	
5	Animal heart	0	22.6	22.1	339	286	15.6
		2	340
		5	22.6	22.6	324	278	14.2
		9	22.7	23.0	325	271	16.6
1	Human heart	0	254	209	17.7
		3	233	165	26.0
1	Human heart	0	170	118	30.6
		4	124	85	31.4
3	Human* heart	0	150	107	28.6
		3	84	37	55.9

* Left in unsterilized containers at room temperature.

TABLE 6.—*Creatine Values in Relation to Postmortem Factors*

Hours Post Mortem	No. of Cases	Left Ventricle, Mg.	Right Ventricle, Mg.	Average Combined Left and Right, Mg.	Difference Between Left and Right	
					Mg.	Per Cent
1- 3.....	16	208.0	163.0	185.5	45.0	21.6
4- 12.....	37	215.8	151.4	183.6	64.4	29.8
13- 24.....	28	202.9	136.4	169.7	66.5	32.3
25- 36.....	4	212.3	143.0	177.7	69.3	32.6
37- 48.....	3	169.3	120.7	145.0	48.6	28.7
49- 96.....	11	168.7	108.7	138.7	61.0	35.6
97-120.....	3	203.0	125.3	164.2	77.7	38.2
1- 36.....	85	209.8	148.2	179.0	61.6	29.4
37-120.....	17	174.9	113.8	144.4	61.1	34.9

at room temperature the average figures showed a decrease of 44 per cent for the left ventricle and of 70 per cent for the right. The decrease was always greater in the right ventricle than in the left.

This variance in behavior between animal and human hearts might be explained on the basis that in man, bacterial action, especially in the right ventricle, may lead to a disappearance of the creatine (Hunter¹⁷).

Subsequent studies revealed that in the 102 cases shown in table 6 the averages of the creatine content of the ventricles did not change

17. Hunter, A.: Creatine and Creatinine, Monographs on Biochemistry, New York, Longmans, Green & Co., 1928.

TABLE 7.—Creatine Content of Human Heart Muscle in 102 Cases

Serial No.	Age, Years	Sex	Creatine Content of Heart				Heart Weight, Gm.	Creatine of Voluntary Muscle, Mg.	Post Mortem, Hours
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Absolute, Mg.	Difference, per Cent			
18	60	M	369	283	86	23.3	500	520	10
115	60	F	348	158	190	54.6	450	564	15
92	46	M	321	176	145	45.2	400	446	8
71	¾	M	278	214	64	23.0	54	343	2½
91	47	M	276	176	100	36.2	375	...	2
99	67	F	275	152	123	44.7	350	308	3
110	22	F	271	176	95	35.0	225	442	11
117	6	M	269	149	120	44.6	75	321	6
39	68	F	265	212	53	20.0	450	456	1
45	78	M	263	150	113	43.0	475	472	15
96	29	M	263	200	63	24.0	175	...	20
25	64	M	259	189	70	26.0	200	...	7
78	44	M	255	151	104	40.8	325	487	8
94	45	M	255	179	76	29.8	300	...	7
105	54	M	254	209	45	17.7	300	437	2
24	29	M	247	181	66	26.7	400	427	5
76	78	M	246	153	93	37.8	425	431	12
79	50	M	246	151	95	36.8	300	379	15
69	58	M	242	157	85	35.1	275	412	34
19	15	M	239	142	97	40.6	200	...	17
36	46	M	237	204	33	13.9	350	428	2
59	43	M	236	196	40	16.9	250	...	7
93	3	M	234	147	87	37.2	100	...	13
111	47	M	233	173	60	25.8	350	397	4
112	44	M	232	164	68	29.3	250	417	6
81	65	M	231	169	62	26.8	375	458	10
21	53	F	231	150	81	35.0	200	...	6
48	29	F	230	195	35	15.2	175	...	7
43	61	M	227	130	97	42.7	300	483	15
41	44	M	226	158	68	30.1	500	452	12
98	83	F	225	142	83	36.9	300	347	19
88	60	F	223	155	68	30.5	350	382	38
23	46	M	222	170	52	23.4	400	433	14
103	33	M	220	144	76	34.5	250	433	16
106	30	F	219	134	85	38.8	325	301	7
28	33	F	219	171	48	21.9	500	319	4
72	67	F	219	107	112	51.1	400	368	15
89	39	M	218	123	95	43.6	600	892	120
74	1½	F	218	176	42	19.3	85	...	3
26	22	M	216	130	86	39.8	275	428	30
95	4	M	207	138	69	33.2	100	...	18
82	49	F	207	163	44	21.3	400	376	3
57	33	M	206	180	26	12.6	325	382	14
90	48	M	205	98	107	52.2	400	387	96
42	75	M	205	119	86	42.0	425	488	10
100	32	M	203	147	56	27.6	375	297	9
22	31	F	200	116	84	42.0	175	393	9
109	35	F	200	143	57	38.5	275	385	8
75	40	M	196	124	72	36.7	600	342	72
108	37	M	196	178	18	9.2	250	462	4
53	62	M	196	112	84	42.9	300	...	108
66	75	M	195	141	54	27.7	450	440	120
34	58	F	195	156	39	20.0	350	324	10
35	26	F	194	146	48	25.0	375	346	19
63	52	M	192	167	25	13.0	300	347	2
64	56	M	192	116	76	39.6	250	487	3
97	50	M	192	178	14	7.3	750	348	1
20	51	M	190	134	56	29.5	225	...	41
54	75	M	190	124	66	34.7	450	...	84
114	33	F	190	140	50	26.3	650	...	4
55	27	M	188	124	64	34.0	400	411	17
73	50	M	188	108	80	42.6	300	...	12
30	50	M	188	127	61	32.4	210	297	11
50	46	F	187	125	62	33.2	300	387	8
62	36	M	184	134	50	27.2	500	410	6
84	69	M	183	163	20	10.9	300	417	20
15	62	M	183	120	63	34.4	750	...	15
87	6	M	182	134	48	26.4	140	320	15
83	60	M	181	104	77	42.5	450	376	24
27	23	F	178	117	61	34.3	275	368	72
116	47	M	178	111	67	37.6	560	348	7
107	55	M	175	116	59	33.7	475	340	66
40	77	M	175	114	61	34.9	600	261	65
47	47	M	174	114	60	34.5	350	...	16
51	53	M	174	135	39	22.4	250	...	8
67	40	M	174	118	56	32.2	250	398	50

TABLE 7.—*Creatine Content of Human Heart Muscle in 102 Cases—Continued*

Serial No.	Age, Years	Sex	Creatine Content of Heart				Heart Weight, Gm.	Creatine of Voluntary Muscle, Mg.	Post Mortem, Hours
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Absolute, Mg.	Difference, per Cent			
16	39	M	171	113	58	33.9	350	...	19
44	50	M	171	93	78	45.6	500	...	12
102	2 mo.	F	170	158	12	7.1	20	369*	3
113	60	M	170	118	52	30.6	500	364	20
32	23	M	170	120	50	29.4	275	310	11
101	61	M	170	106	64	37.6	350	398	16
68	56	M	169	102	67	39.6	500	452	48
70	42	M	168	130	38	22.6	300	330	32
85	54	M	165	98	67	40.6	350	327	72
52	36	M	163	134	29	17.8	300	427	3
17	77	M	163	127	36	22.1	375	...	3
86	76	M	162	153	9	5.6	400	397	20
58	55	M	160	100	60	37.5	350	418	24
65	58	M	160	124	36	22.5	450	...	4
29	43	F	158	120	38	24.1	275	282	12
31	68	M	152	144	8	5.3	500	339	20
49	50	M	149	126	23	15.4	475	393	48
104	56	M	148	117	31	20.9	925	275	72
60	60	F	146	109	37	25.3	825	...	14
46	46	M	145	112	33	22.8	400	...	22
77	N.B.	F	143	148	-5	-3.5	20	296	6
80	52	M	142	88	54	38.0	325	364	66
38	43	M	138	114	24	17.4	275	367	12
33	35	F	130	113	17	13.1	375	...	3
61	52	F	116	112	4	3.4	350	...	2
56	62	M	108	82	26	24.1	250	258	72

* Illopoas muscle.

significantly within thirty-six hours post mortem. Furthermore, although there was a decrease in the absolute values after thirty-six hours, the drop in the creatine content of the right ventricle appeared earlier and was greater than that of the left; therefore the difference between the values for the left and the right ventricles was practically unaltered.

However, in order that the factors mentioned might be excluded, only the 85 specimens which were examined within thirty-six hours post mortem were used in the summarizing tables.

B. Data on Ventricles.—Table 7 gives the findings on the creatine content of the left and the right ventricles (determined by the trinitrophenol precipitation method) in the series of 102 human hearts and also the other data used for the correlation tables. In every case except that of the new-born, the creatine concentration in the left ventricle was higher than that in the right. This case was omitted in the summarizing tables. In the correlation tables, the data on 17 hearts examined after thirty-six hours post mortem were omitted to eliminate the factors of autolysis and postmortem errors.

The distribution of the 84 hearts grouped according to 50 mg. variations of creatine values is shown in table 8. The absolute figures varied between 93 and 369 mg. for both ventricles. The left ventricle in 76 of 84 hearts showed a range of from 150 to 300 mg.; the right ventricle

in 77 gave a range of from 100 to 200 mg. The average combined creatine content of the left and the right ventricles showed that 82 gave creatine values between 100 and 250 mg.

In table 9, the data on 84 hearts are summarized according to range, mean and average values of creatine content of each ventricle. The

TABLE 8.—*Creatine Content of Left and Right Ventricular Heart Muscle*

Range, Mg. per 100 Gm.	Distribution in 84 Hearts		
	Left Ventricle	Right Ventricle	Average Combined Left and Right Ventricles
93-99.....	0	1	0
100-149.....	5	44	21
150-199.....	33	33	42
200-249.....	31	5	19
250-299.....	12	1	1
300-349.....	2	0	1
350-369.....	1	0	0

TABLE 9.—*Creatine Content of Right and Left Ventricles in 84 Hearts**

	Left Ventricle	Right Ventricle
Range.....	116 to 369	93 to 283
Mean.....	243	188
Average.....	211	148

* Milligrams of creatine per hundred grams of wet muscle.

TABLE 10.—*Distribution of Cases According to Percentage Differences of Right and Left Ventricles*

Percentage Difference, Left and Right	Number of Hearts
3-9.....	6
10-19.....	11
20-29.....	27
30-39.....	26
40-49.....	12
50-55.....	2

range for the left ventricle was from 116 to 369 mg. with an average of 211 mg., and the range for the right was from 93 to 283 mg. with an average of 148 mg.

Table 10 shows the distribution of creatine in 84 hearts according to percentage differences between the left and the right ventricles. The differences ranged from 3 to 55 per cent. Of the 84 hearts, 78 (or 93 per cent) gave differences of over 10 per cent, outside the range of experimental error.

Table 11 summarizes the absolute and percentage differences between the left and the right ventricles. The percentage differences

were calculated by using the left ventricles (with the higher figure) as the standard. The average difference between left and right ventricles was 63 mg., or 30 per cent.

The findings in the 9 animal hearts are given in table 4, which, summarized in table 12, shows the range of absolute values to be from 266 to 379 for the left ventricle, or an average of 308, and from 208

TABLE 11.—*Differences Between Creatine Content of Right and Left Ventricles*

	Absolute Difference, Mg. per 100 Gm.	Absolute Difference, per Cent
Range of 84 hearts.....	4 to 190	3 to 55
Mean.....	97	29
Average.....	63	30

TABLE 12.—*Creatine in Left and Right Ventricles of 9 Animal Hearts **

	Left Ventricle, Mg.	Right Ventricle, Mg.	Difference Between Left and Right	
			Mg.	Per Cent
Range.....	266 to 379	208 to 328	23 to 75	8.6 to 21.9
Mean.....	322.5	268.0	49	15.3
Average.....	308.2	263.2	45	14.6

* Milligrams of creatine per hundred grams of fresh muscle.

TABLE 13.—*Relationship Between Age and Creatine Values in 85 Hearts*

Age Range	Number of Cases	Ventricle			Absolute Difference	
		Left, Mg.	Right, Mg.	Average Combined Left and Right, Mg.	Mg.	Per Cent
New-born	1	143	148	146	—5	—4
New-born to 1	2	224	186	205	38	17
1 to 15	6	225	148	186	77	34
16 to 30	9	221	156	189	65	29
31 to 50	35	203	146	175	57	28
51 to 70	26	212	148	180	65	30
71 to 83	6	211	141	176	70	33

to 328, or an average of 265 for the right ventricle. Table 12 also shows that the range of difference between left and right ventricles was from 23 to 75 mg., or from 8.6 to 21.9 per cent with an average of 43 mg., or 14 per cent.

C. Correlation Data.—On correlating the findings in the human hearts with other available data, it is found that in relation to age as shown in table 13 at birth there is little difference between the creatine content of the left and right ventricle, and that the values are decidedly lower than those obtained shortly after birth. Within the first year the figures for both ventricles reach a maximum. There is essentially

no change up to the thirty year period. In the age period from 30 to 50 there is a definite drop in the creatine content of both ventricles, but with further increasing age there is again an increase. It is further of interest that the difference rises during the growth period (from 1 to 15 years) to 34 per cent, falls in the age period from 30 to 50 to 28 per cent, but again rises with increasing age to 33 per cent.

Correlating the creatine content with heart weight, some very interesting findings are noted (table 14). In the infants with hearts of 50 Gm. or under the creatine content is low. The maximum values are found in hearts weighing from 50 to 150 Gm. During the increase of weight up to 250 Gm., i. e., growth hypertrophy, the actual values are practically unchanged, but there is a decrease in the percentage difference (from 37 to 29 per cent). A further increase in weight from 250 to 350 Gm., which may be regarded as a physiologic hypertrophy, shows

TABLE 14.—*Relationship Between Heart Weight and Creatine Content in 85 Hearts*

Heart Weight, Range	Number of Cases	Ventricle		Average Combined Left and Right, Mg.	Absolute Difference, Left—Right	
		Left, Mg.	Right, Mg.		Mg.	Per Cent
20 to 50	2	157	153	155	4	2
51 to 150	6	231	159	195	72	37
151 to 250	14	224	159	191	65	29
251 to 350	30	202	143	172	59	29
351 to 450	20	216	147	181	69	32
451 to 550	8	219	156	188	63	29
551+	5	178	132	155	46	26

some decrease in the absolute figures while the percentage difference remains constant. With hypertrophy from 350 to 450 Gm., there is a rise in both the absolute values of each ventricle and the percentage difference (from 29 to 32 per cent). With the beginning of a definite pathologic hypertrophy (weights above 450 Gm.), there is a slight increase in absolute values for both ventricles while the percentage difference falls (from 32 to 29 per cent). Beyond 550 Gm. the absolute values fall to figures found in early infancy, with a fall in the percentage difference (from 29 to 26 per cent).

The pectoralis major, because it was easily obtained at autopsy, was used as the voluntary muscle for comparing the creatine values of cardiac and voluntary muscles. Table 15 shows the findings in 60 cases. The voluntary muscle figure ranged from 258 to 564 mg., giving an average of 394 mg. All but 5 of the 60 gave values between 300 and 500 mg. The per cent of solid ranged from 21.5 to 27.9, an average of 24.4.

The observations of Myers and Fine^s on the rabbit would lead one to believe that the creatine content of voluntary muscle in a given species

is relatively constant under normal conditions. How is one to account for the rather wide fluctuations encountered in the 60 human hearts recorded in table 15? The low figures might be accounted for by the fact that the patients had been in a state of cachexia for some time prior to death, and this appears to have been the case, but high values for the creatine content of the voluntary muscle are not so readily explained. It has been shown, however, that the creatine content of muscle may be raised by administration of creatine and creatinine. By intravenous injection of creatine in cats, Folin and Denis¹⁸ produced a temporary increase of from 9.2 to 26.6 per cent (in 1 case, 70 per cent) in the creatine content of the voluntary muscle. Similarly, Myers and Fine¹⁹ reported a less pronounced increase of about 5 per cent in rabbits on subcutaneous injection of creatine (and also creatinine). More recently Chanutin and Beard²⁰ were able to produce an increase of from 5 to

TABLE 15.—*Comparison of Creatine Content of Voluntary and Cardiac Muscle*

Number of Cases in Group	Voluntary Muscle		Ventricular Muscle		
	Range,* Mg.	Average, Mg.	Average Left, Mg.	Average Right, Mg.	Average Combined Left and Right, Mg.
10	282-321	305	202	140	171
10	324-364	344	194	151	173
10	367-393	380	201	136	168
10	397-427	410	200	146	173
10	427-452	436	248	163	199
10	456-564	488	255	167	209

* Average creatine value for voluntary muscle in the 60 cases was 394 mg. per hundred grams.

10 per cent in the creatine content of the muscle of the mouse by adding creatine to the diet. It is therefore possible to raise the creatine level of voluntary muscle by the administration of creatine and creatinine, and this fact would suggest that the retention of creatinine in renal disease should bring about an increase in the creatine content of both voluntary and cardiac muscle.

The 60 cases in table 15 have been arranged according to the magnitude of the creatine content of the voluntary muscle, and the averages

18. Folin, O., and Denis, W.: Protein Metabolism from the Standpoint of Blood and Tissue Analysis: III. Further Absorption Experiments with Especial Reference to the Behavior of Creatine and Creatinine and to the Formation of Urea, *J. Biol. Chem.* **12**:141, 1912. VII. An Interpretation of Creatine and Creatinine in Relation to Animal Metabolism, *J. Biol. Chem.* **17**:493, 1913-1914.

19. Myers, V. C., and Fine, M. S.: The Influence of the Administration of Creatine and Creatinine on the Creatine Content of Muscle, *J. Biol. Chem.* **16**:169, 1913.

20. Chanutin, A., and Beard, H. H.: A Study on the Effect of Feeding Creatine on Growth and Its Distribution in the Liver and Muscle of Normal Mice, *J. Biol. Chem.* **78**:167 (June) 1928.

are given for groups of 10. One may assume on the basis of data in the literature that the normal creatine content of voluntary muscle in man is close to 400 mg. It will be noted that the creatine content of the left ventricle remains fairly constant at close to 200 mg. in the first four groups, but that as soon as the creatine content of the voluntary muscle begins to rise above the assumed saturation point of about 400 mg. there is likewise a corresponding rise in the creatine content of the cardiac muscle. The cause of the relatively higher creatine values in the voluntary muscle in the last 20 of the 60 hearts is not entirely clear, but it is evident that renal insufficiency was the important factor in a number of them. In the last group of 10 hearts, 5 of the patients suffered from arteriolar nephrosclerosis, 3 from pneumonia, 1 from pyelitis and generalized arteriosclerosis and 1 from Banti's disease and emphysema. It might be further noted that the last 2 hearts in this group of 10 were the first two (nos. 18 and 115) mentioned in the general table 7, and had the highest content of creatine in the left ventricle and voluntary muscle of any of the specimens in the series. Both cases showed arteriolar nephrosclerosis and cardiac hypertrophy and dilatation at autopsy.

Unfortunately the determination of the blood creatinine was made in only 1 of these cases (no. 18) and was found to be 25.1 mg. One of us (V. C. M.) has repeatedly noted that in persons suffering from arteriolar nephrosclerosis the blood creatinine may be excessively high in proportion to the urea. Obviously, this marked retention of creatinine not only would raise the figure for the creatine in the muscle by the amount of the preformed creatinine, but would tend to shift the equilibrium between creatine and creatinine toward the creatine side, and thus raise the true values for creatine in the muscle as well. There would appear to be little doubt that this was the explanation for the very high creatine content of both voluntary and cardiac muscle in these 2 cases (nos. 18 and 115). This is a problem which we are studying further at the present time, and hope to discuss in another paper in the near future. We have considered this question here because of its possible bearing on our present problem, but it is quite clear that the difference between the right and the left ventricular muscles persists through all the fluctuations of the absolute values as shown in the table.

COMMENT

A. Significance of Findings.—It should be pointed out that our studies on the creatine of the individual ventricles were carried out independently, i. e., without any knowledge of prior work along these lines, and, as previously indicated, were undertaken not as isolated chemical investigations or for the correlations of the creatine values of the heart in association with other problems on creatine metabolism, but primarily for their value in regard to the concept that the left and right

ventricles were qualitatively different muscles. The data are of twofold significance. First, they reveal differences in the creatine content of the two ventricles of the heart; second, they serve to confirm the concept that the ventricular muscles are qualitatively different.

There are references pertaining to the creatine content of the "heart." These refer to the organ as a whole, or imply that the figures given are applicable to the "heart" when analyses were carried out on samples of the left ventricle only (Katz²¹), and in some the exact regions of the heart examined are not specified.

As far as we have been able to determine from a search of the literature (after our work was well under way) there are only two previous references to creatine determinations carried out separately on the different portions of the heart.

Constabel,²² on examining 38 human hearts at autopsy (hours post mortem not specified), found a difference of 10 per cent between the left and the right ventricle to be general. In 2 hearts with left ventricular hypertrophy (due to aortic insufficiency), the differences were 20 per cent (160 left and 128 right) and 26 per cent (175 left and 130 right). Moreover, he could find no correlation between the creatine content of the heart and age and sex. He stated that he believes that when the heart action is good the creatine content is high, but when the action is weak, especially in fatty changes, the creatine content is low. (Since the absolute figures were never above 200 mg. per hundred cubic centimeters, we believe that he worked with hearts obtained many hours post mortem.)

Vollmer²³ determined the phosphoric acid and creatine content of five different portions of the heart and found for the ventricles averages of 221 mg. for the left and 173 mg. for the right, or a difference of 21 per cent. Moreover, he found that both the creatine and the phosphoric acid contents of the ventricles were higher than that of the auricles. Zondek, Kraus and Wolheim found differences in potassium and calcium between auricles and ventricles. Vollmer warned, however, against drawing physiologic deductions from these chemical differences, since the latter may be due to variations of the connective tissue, elastic fibers, fat content, vascular supply and innervation of the different portions of the heart. He also studied postmortem effects and stated that Riesser¹⁵

21. Katz, L. N.: The Asynchronism of Right and Left Ventricular Contractions and the Independent Variations in Their Duration, *Am. J. Physiol.* **72**:655, 1925.

22. Constabel, F.: Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszuständen, *Biochem. Ztschr.* **122**:152, 1921.

23. Vollmer, H.: Untersuchungen über den Kreatin- und Phosphorsäuregehalt verschiedener Herzteile, *Ztschr. f. d. ges. exper. Med.* **65**:522, 1929.

found no significant change in creatine up to forty-eight hours; in his own experiments he found a drop of 5 per cent in twenty-four hours and 3 per cent in the next twenty-four hours, or 8 per cent for the entire forty-eight hours.

Our findings on the creatine differences of the two ventricles confirm and extend the findings of Constabel and Vollmer.

B. Significance of the Differences Between the Ventricles.—In a series of 85 human hearts examined within thirty-six hours post mortem the creatine content of the left ventricle was found to be greater than that of the right in all cases except 1 (in a new-born infant). For the series, the creatine content of the left ventricle averaged 30 per cent more than the right. In a series of 9 fresh animal (cattle) hearts, the left ventricle showed a higher creatine content than the right in every case, and for the series the content of the left ventricle averaged 14 per cent higher than that of the right. The smaller difference in the animals, if not due to variation of species, may well be due to the fact that there were no abnormal hearts, i. e., hearts with hypertrophied ventricles. Constabel²² found the left ventricle to be 10 per cent higher in "normal" hearts and from 20 to 26 per cent higher in hypertrophied hearts. Vollmer found the left ventricle to be 21 per cent higher.

These differences are not as great as between the light and the dark muscle of birds, or between voluntary, cardiac and smooth muscle in a given animal, but they are of the same magnitude as exists among the different skeletal muscles in the same body (Riesser,¹⁵ Ferdmann and Feinschmidt²⁴). Vollmer²³ believed that the differences in creatine content of the two ventricles might not have any physiologic significance but might be due in part to variations of fatty, fibrous and elastic tissue, blood supply, innervation and water content. This view is not justified, since it is not only in creatine content but in other elements that the two ventricles differ. Differences in glycogen, lipids, phosphoric acid (Vollmer), inorganic salts, potassium and calcium have been recorded. Wearn²⁵ showed variations in the number of capillaries of different portions of the heart in man and in animals. There are electrocardiographic differences between the ventricles which may again indicate qualitative differences between the left and the right ventricles. And there are probably other differences with which we are not acquainted.

Moreover, it is conceivable that the differences in the very fatty, fibrous, elastic tissue, blood supply, innervation and water content, indicate that the two ventricles may be regarded as different muscles.

24. Ferdmann, D., and Feinschmidt, O.: Zur Frage der Verteilung der Kreatinphosphorsäure in verschiedenen Muskeln und Organen des tierischen Organismus, *Ztschr. f. physiol. Chem.* **178**:173, 1928.

25. Wearn, J. T.: The Extent of the Capillary Bed of the Heart, *J. Exper. Med.* **47**:273, 1928.

The creatine contents of various muscles in the same animal and "comparable" muscles in different species of animals vary and probably in association with functional activities. Palladin and Ferdmann²⁶ showed in voluntary muscle under "training" an increase in creatine content of from 10 to 20 per cent.

The practical point is that the differences in creatine exist. It is beyond the scope of this communication to enter into a discussion or to review the available knowledge on creatine and its rôle in muscular activity. Excellent comprehensive reviews are those of Hunter,¹⁷ Milroy,²⁷ and Myers.²⁸ It is now fairly well established that creatine, as phosphocreatine, plays an active rôle in muscular contraction.

While we were planning studies to obtain evidence that functional differences exist between the muscles of the two ventricles, Dr. Harold Feil called our attention to the fact that it was available in the works of Katz.²¹ Having established, beyond any doubt, that there was an asynchronism between the two ventricles, Katz, by a brilliant analysis of his data, concluded that the asynchronism could not be accounted for, entirely, by merely physical factors such as differences in pressure, tension and volume in the ventricular chambers, but that some unknown factors were involved. Our analysis of his findings leads us to believe that the explanation for the asynchronism and the electrocardiographic findings lies in the fact that the two muscles are qualitatively different, and we venture to suggest that some of the irreconcilable variations of the asynchronism may be due to age factors which seem to modify the qualitative differences between the muscles of the two ventricles.

In this connection it is of interest to point out that from what is known regarding the relationship between creatine content and muscular contraction it could be predicted that since the left ventricle has a higher creatine content (light versus dark muscle) its contractions should be faster, more energetic, etc., and curiously enough the findings of Katz confirm this prediction.

It is possible that any factor which alters the creatine content of the heart may alter its action, and in view of the normally different creatine contents, the added variations may disturb anew the conditions prevailing. Moreover, as is known for the skeletal muscles in the "myopathies," since single groups of muscles are affected, it is conceivable that in the heart, one or the other of the chambers may be affected by different increases or decreases of creatine in various diseases. It is possible that

26. Palladin, A., and Ferdmann, D.: Ueber den Einfluss des Trainings auf den Kreatingehalt der Muskeln, *Klin. Wchnschr.* **6**:2386, 1927.

27. Milroy, T. H.: The Present Status of the Chemistry of Skeletal Muscular Contraction, *Physiol. Rev.* **11**:515 (Oct.) 1931.

28. Myers, V. C.: Creatine and Creatinine, *Yale J. Biol. & Med.* **4**:467 (March) 1932.

some of the cardiac (and other muscular) abnormalities seen in fevers, metabolic disturbances, etc., may be due to chemical alterations, especially if only one of the ventricles is affected.

The realization that the left and right ventricles (as well as other portions) of the heart are chemically different may have some value in pharmacologic and therapeutic measures as applied to the heart. It would be of interest to attempt to correlate the effects of various drugs acting on the heart with the chemical alterations these may invoke along the lines done for voluntary muscle by Masayama and Riesser.²⁹ It may be found beneficial to administer along with other cardiac stimulants in heart "failure," as in the myopathies, creatine or some of its precursors.

III. The New Concept: In summarizing his embryologic findings on the bulbus cordis, Keith, in 1924, stated: "My aim will be to demonstrate the parts of the ventricle formed out of this element and to show reason why separate consideration must be given to these parts in all our attempts to unravel the exact mechanism of the ventricular pump." To paraphrase Keith, we believe there is sufficient evidence at hand to state that separate consideration must be given to the right and left ventricles in all our attempts to unravel the exact mechanism of the ventricular pump.

The fact is that the heart is not a single muscle but is made up of separate bundles, each with attachments at the valvular orifices at the base and in the regions of the papillary muscles. One of us (D. P. S.) has undertaken studies on these individual bundles, but progress has been delayed by technical difficulties. It is hoped that the investigation will be completed in the near future. The preliminary findings indicate that it may be shown ultimately that there are differences between these individual muscle bundles. Just as there occur degenerations, inflammations and hypertrophies of one ventricle and not the other, it appears that lesions may occur in single muscle bundles and that some of the perplexing problems of the heart may be due to disturbances of the individual muscle bundles.

The concept that the two ventricles are different offers a working theory which may reconcile, in a manner better than has been possible heretofore, the functional activities with the structure and chemical constitution of the heart. As such its value remains to be proved or disproved.

It should be pointed out that at present the concept may be of practical application, although it does not answer the question as to whether these differences between the ventricles (or the muscle bundles) are

29. Masayama, T., and Riesser, O.: Ueber die Beziehungen des Glykogens zu Kreatin und Kreatinphosphorsäure im Kaninchenmuskel, *Biochem. Ztschr.* **234**: 323, 1931.

inherent, i. e., developmentally or originally qualitatively different or acquired after birth, owing to the greater amount of work done by the left ventricle (or single muscle bundles).

SUMMARY AND CONCLUSIONS

It has been established that the concentrations of creatine of the left and right ventricular muscles of the heart are different, the former having the greater concentration. Attention has also been called to correlations between creatine content and age and weight of the heart. From the standpoint of creatine-creatinine metabolism, it is significant that when the creatine content of voluntary muscle exceeds about 400 mg. (the probable saturation point) a corresponding elevation in the cardiac muscle also occurs, and further, that the retention of creatinine in renal disease has an augmenting influence on the creatine content of both cardiac and voluntary muscle.

In addition to embryologic, anatomic, physiologic and pathologic observations, chemical evidence is now presented pointing to the fact that the left and right ventricles are different muscles.

These differences justify the concept that the heart is not a uniform muscle but that it is made up of several qualitatively different muscles. The significance and possible practical value of this concept are discussed.

THORACIC STOMACH

REPORT OF FIVE CASES

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In September, 1931, in a patient who had been under observation for some years, there suddenly developed severe symptoms suggestive of obstruction high up in the gastro-intestinal tract. The patient was admitted to the New England Deaconess Hospital. A roentgenogram showed that two thirds of her stomach was in the thoracic cavity. The diagnosis of hernia of the stomach through the diaphragm, with obstruction at the pylorus, was made. The details will be given in the first case that we report. Treatment was without avail, and the patient died.

Fortunately a postmortem examination was permitted, and several unusual things were found. Two thirds of the stomach was in the thoracic cavity as the roentgenograms had indicated. Of greater importance, however, was the anatomic finding of an esophagus that was foreshortened by at least 4 cm and probably more. The significance of this short esophagus was overlooked at the time, and we all considered the diagnosis to be hernia of the stomach through the diaphragm.

This patient had complained for some considerable time of a peculiar type of dyspnea, to be described later, which we could never explain to our own satisfaction. On finding so large a part of the stomach in the thorax, the cause of dyspnea was evident. We recalled the cases of two other patients with the same type of dyspnea for which we had been unable to find any adequate reason. They were sent for and examined roentgenologically at the hospital with a special request that the length of the esophagus be determined. In these two cases the entire stomach was found to be in the thorax, and the esophagus in each case was found to be foreshortened. By this time it was evident that we were not dealing with hernia but with a congenital foreshortening of the esophagus which had prevented the descent of the stomach from the thorax, where it normally develops, into the abdominal cavity where it is normally found.

This was a clinical condition that was entirely unfamiliar to us. We could find no reference to it in the most recent textbooks, and we felt that we had recognized a condition that had escaped previous observation. However, in a review of the literature on "hernia of the dia-

phragm" we have been able to find seven similar cases reported. By far the most important case is the one reported by Bailey¹ in 1919. He found, during the regular dissection of the body of a man, 77 years of age, that the entire stomach was in the thoracic cavity and that the esophagus ended at the level of the third costal cartilage instead of extending to the normal level of the tenth thoracic vertebra.

So important are his findings that we repeat some of the pertinent facts:

Upon opening the abdominal cavity we found only the pyloric antrum projecting through the esophageal opening of the diaphragm for a distance of 6 cm. Upon opening the thorax, the stomach, which was entirely in the thoracic cavity, was found lying between the pleural cavities, and behind the pericardium in the posterior mediastinum. The stomach was completely surrounded with a serous sac consisting of the normal peritoneal pockets of the stomach.

He recognized the fact that this was in no sense a hernia and that the stomach had developed in the thorax. He explained the existence of the sac by the fact that the peritoneal pockets of the stomach develop before the stomach and the diaphragm begin their descent. When the diaphragm descended, it left behind it the stomach, which was anchored by the esophagus, and from necessity elongated these peritoneal pockets which remained continuous with the peritoneal cavity. He gave the name of thoracic stomach to this condition.

So far as he could determine from his review of the literature, he was the first to recognize this condition. Our own review would seem to confirm this view although we are not sure but that the short esophagus was observed in some of the early reported cases of hernia of the diaphragm and that the significance was overlooked. Attention should also be called to an article by Brun, Masselot and Jaubert de Beaujeu² published in 1922 in which they reported finding by roentgen rays a case of "non-descent of the stomach with inversion, the movement of rotation around the vertical axis being towards the right instead of the left." Unfortunately they made no observations as to the length of the esophagus.

About five years after Bailey's report was published, LeWald³ wrote an excellent article from the point of view of the roentgenologist, entitled "Thoracic Stomach: Differentiation from Eventration and Hernia of the Diaphragm." In this article he described two cases of thoracic stomach. Since then Roberts⁴ has reported one case, Morris⁵

1. Bailey, P.: A Case of Thoracic Stomach, *Anat. Rec.* **17**:107, 1919.

2. Brun, Masselot and Jaubert de Beaujeu: *J. de radiol. et d'électrol.* **6**:278, 1922.

3. LeWald, L. T.: Thoracic Stomach: Differentiation from Eventration and Hernia of Diaphragm, *Radiology* **3**:91, 1924.

4. Roberts: *Brit. J. Radiol.* **32**:17, 1927.

5. Morris, H.: Case of Thoracic Stomach, *Radiology* **13**:265, 1929.

one case. Weitzen⁶ one case and Lyons⁷ one case. Lyons, however, missed the significance of the foreshortened esophagus as he made the diagnosis of "diaphragmatic hernia, thoracic stomach."

Without question Bailey¹ deserves the credit of calling attention to the fact that thoracic stomach is a definite clinical entity. We can find no instance in the literature in which the internist or the surgeon has recognized the condition. In reporting our five cases, the largest number yet reported in a single series, we believe that we are calling attention for the first time to the clinical significance of its recognition as a definite entity. In four of our five cases it was possible to make a probable clinical diagnosis of thoracic stomach before the roentgenologic diagnosis was made.

REPORT OF CASES

CASE 1.—A woman, aged 60, had been under our observation for some years for minor complaints. For two or three years she had a low grade secondary anemia which did not respond to treatment.

One year before her admission to the hospital she complained of dyspnea that had been developing and increasing for about a year. This dyspnea was of a panting type, like that seen in one who has been running. As she came into the office and sat down, we observed the dyspnea and asked her whether she had been running. She replied, "Wait a minute until I get my breath, and I will tell you about it." At the time the pulse rate was 94. Her breathing became normal in a few minutes, and she gave her history. The attack which we observed was brought on by the effort of walking from her car into the office. Any ordinary exertion about the house brought it on. It was more marked after eating, and she had learned from personal experience to eat small meals and to keep quiet for some time afterward.

Her previous history, so far as it pertained to this condition, was as follows: As far back as she could remember, she could not overeat and be comfortable. When she ate too heavy or too highly spiced foods or when she drank too much liquid with a meal she would feel so "stuffed" that she would regurgitate a part of the meal. Occasionally she would force herself to vomit, and this gave prompt relief. Nausea was not present as a rule but did occur at times. There was no gas, gastric distress or any other symptom of indigestion. As soon as she regurgitated or vomited she felt as well as ever. She had never considered that she had indigestion and had never consulted a physician for indigestion.

Physical examination at this time gave negative results. Her weight was 175 pounds (78.28 Kg.); her height, 5 feet and 8 inches (188.7 cm.). She had gained 10 pounds (4.53 Kg.) in the past year. The electrocardiogram showed a left ventricular preponderance but revealed no other abnormalities. Examination of the lungs gave negative results. The blood pressure was 165 systolic and 105 diastolic.

Three months before this examination she had been under observation at a well known sanatorium. Gastro-enteric roentgenograms were not made, but she was told that the flat plate of her chest showed an enlarged heart. We were unable

6. Weitzen, M.: Diaphragmatic Hernia with Severe Anemia, *Am. J. Roentgenol.* **28**:808, 1932.

7. Lyons, C. G.: Thoracic Stomach, *Am. J. Roentgenol.* **23**:67, 1930.

to demonstrate any enlargement by percussion. The apparent enlargement of the left border of the heart was evidently formed by the shadow of the thoracic stomach.

We reduced her weight 10 pounds without bringing about any relief of her symptoms. Soon after she began to complain of palpitation as well as of dyspnea. After completing this reduction we did not see her again until the onset of her last illness.

Ten days prior to her admission to the hospital on Sept. 11, 1931, she was seized with severe cramps in the upper part of the abdomen, associated with nausea and vomiting. She was at a summer resort at the time, and the local physician who was called made a diagnosis of food poisoning. Castor oil was

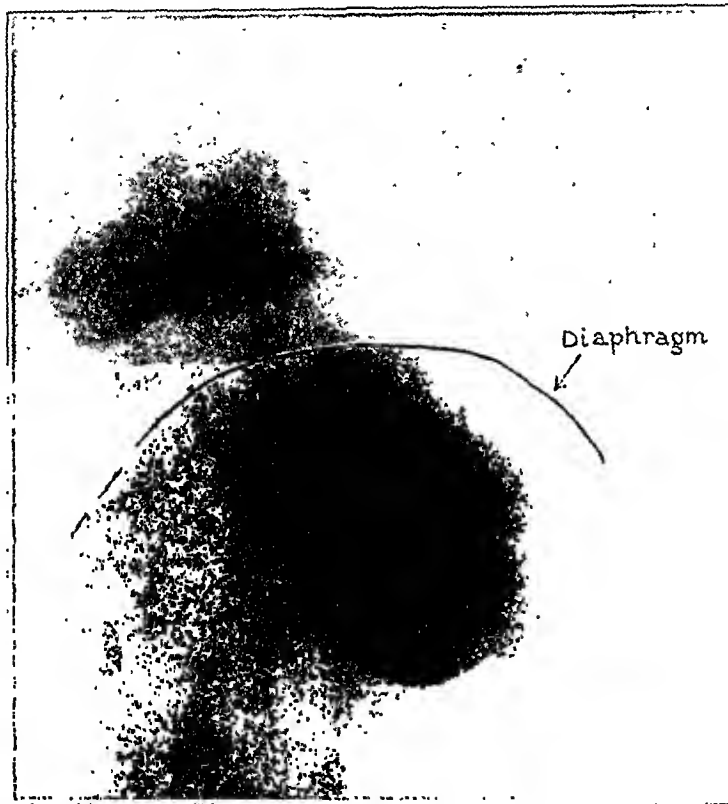


Fig. 1.—Lateral view of stomach of patient 1. Two thirds of the stomach is above the diaphragm. The patient was so ill that the length of the esophagus could not be demonstrated by roentgenograms, but at autopsy it was found to be foreshortened.

given, and the bowels moved freely, without relief from the pain in the epigastrium. The condition gradually but steadily became worse. For thirty-six hours before her admission to the hospital she had been unable to keep anything in her stomach; the pain in the epigastrium was extreme; there was frequent vomiting, and on the morning of her admission she vomited a little blood.

At the time of admission she was in a state of extreme exhaustion and was quite dehydrated. There were constant nausea and vomiting. The bowels had been moving, and gas was being passed without difficulty. There was no distention or tenderness of the abdomen, and no masses were found by palpation. The heart and lungs were normal. The temperature was 99 F., the pulse rate 90, and

the respiratory rate, 18 per minute. A diagnosis of obstruction high up in the digestive tract was made. Critical though her condition seemed, we thought it practical to attempt a careful roentgen examination. This was done, and two thirds of her stomach was found to be in the thoracic cavity. The diagnosis of hernia of the stomach through the diaphragm with obstruction at the pylorus was made. There had, however, been no history of fall, accident or undue strain.

A left phrenectomy and a jejunostomy were performed on Sept. 15, 1931, but this was not followed by any relief of the symptoms, and she died on the following day.

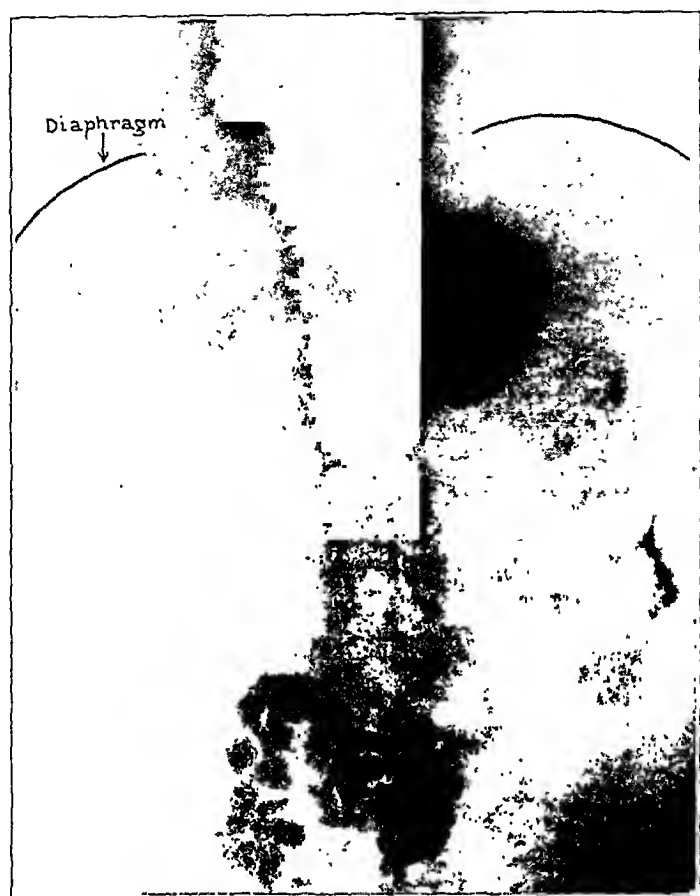


Fig. 2 (case 1).—Anteroposterior view. Two thirds of the stomach is above the diaphragm. The roentgenogram is shown as evidence that there is no indication of the obstructing duodenal ulcer, except that the barium did not pass through the pylorus.

At necropsy it was found that two thirds of the stomach was in the thoracic cavity. The esophagus was foreshortened by at least 4 cm., and probably more. There was a sharply demarcated ulcer, 1 cm. in diameter, situated on the posterior wall of the pylorus; this had caused the obstruction and brought about the patient's death. There was a sac present which consisted, as in Bailey's¹ case, of the normal peritoneal pockets of the stomach.

Four important points in connection with this examination should be noted: 1. None of us present at the necropsy recognized the sig-

nificance of the short esophagus at the time. We believed this to be a case of hernia of the stomach through the esophageal opening of the diaphragm. 2. Roentgen examination failed to give any suggestion of ulcer of the duodenum. 3. An ulcer of the duodenum was revealed that had never given any symptoms until it caused an obstruction. 4. The greater part of the stomach was found above the diaphragm, which explained the dyspnea and subsequent palpitation. Our interest, at the moment, was centered on this last fact, as we recalled the two other patients with a similar type of dyspnea in whom no satisfactory diagnosis could be made.

Both of these patients, as we have noted, were sent to the hospital with a request for a special examination for the determination of the length of the esophagus and the determination of the position of the stomach. Both proved to have thoracic stomach. The histories were as follows:

CASE 2.—The patient, a woman, was 68 years of age when the diagnosis was made. She first came under observation at the age of 56, complaining of dyspnea on slight exertion, of a year's duration; this was increasing in intensity until, at the time she was seen, she was short of breath on very slight exertion. When she sat down, it quickly passed away. At the time her weight was 177 pounds (80.28 Kg.) and her height, 5 feet and 1 inch (154.9 cm.). She had gained 10 pounds in the past year.

The history relating to the digestive function was as follows: As long as she could remember, she had had a sense of substernal fulness if she overate. When this occurred she would frequently regurgitate a little food, without nausea or any distress; occasionally she would vomit the entire meal and feel relieved. She stated that she never had indigestion.

As she came into the office she presented the same type of "panting" as that presented by the first patient, and she, too, said, "Wait a moment until I get my breath." Her pulse rate at the time was 80. In a few moments her breathing was normal, and she gave her history. A thorough physical examination failed to reveal any cause for the dyspnea except her possible obesity. Reduction in weight, however, failed to relieve her symptoms in any degree.

She was not seen again for five years, owing to a change in residence, and at this time she was 61 years of age. At this visit she complained of dyspnea which was more marked than before. Her history during this interval was as follows: Two years previously she had experienced for the first time substernal oppression if she overate; this was promptly relieved by vomiting. There was no nausea, gas or any other symptom of indigestion. Six months later, after a hearty meal she had a sudden attack of severe pain in the left side of the neck and the left shoulder, which extended down the left arm. The pain was "terrific" for ten or fifteen minutes; then she vomited the entire meal with an immediate relief of the acute symptoms, but it was several hours before she felt normal again. During the attack the breathing was labored, and there was marked palpitation. During the succeeding six months she had six or seven similar attacks, all as severe as the first, and they all occurred after "overloading her stomach." They were all relieved by vomiting. There had been no recurrence of the attacks during the past year, as she had learned not to overeat. Three physicians had seen her in these attacks; one diagnosed the condition acute indigestion, and the

other two, angina pectoris. Roentgenograms had been taken, but no satisfactory explanation was found. Physical examination at this time failed to show any satisfactory cause for her dyspnea.

On request she was examined roentgenologically again with the thought of a probable thoracic stomach. The roentgenogram showed the entire stomach above the diaphragm. The fluoroscope demonstrated the esophagus entering the stomach at the level of the ninth thoracic vertebra. The pylorus alone extended through the esophageal opening. The stomach appeared to be considerably dilated.

This case was complicated by a hernia of the colon, probably through the esophageal opening of the diaphragm, as was demonstrated by a barium sulphate enema. The colon extended to the left, nearly to the costophrenic angle, and then looped back to the midline, meeting the hepatic flexure at the esophageal opening.

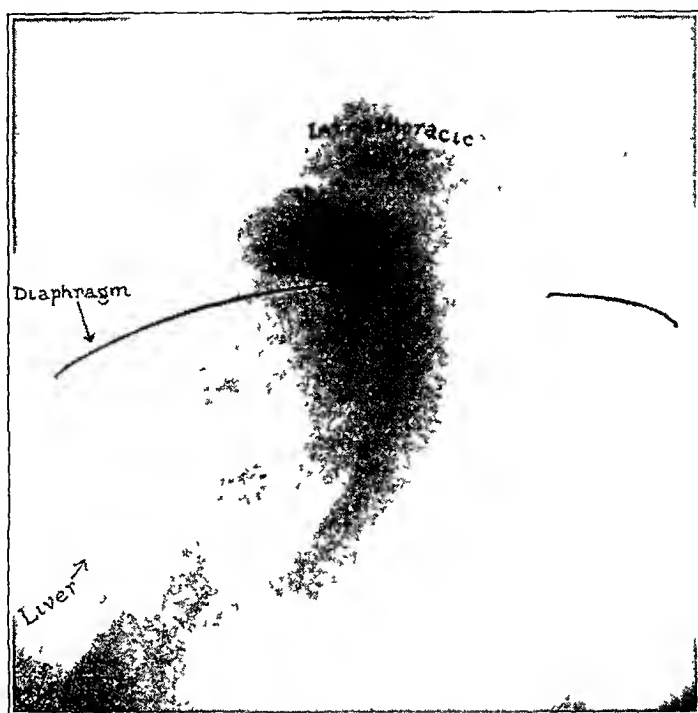


Fig. 3 (case 2).—A large portion of the colon is in the pleural cavity.

CASE 3.—A woman, 68 years of age, was referred to us in 1920 for dyspnea of eight months' duration "due to obesity" and for the purpose of reducing her weight. She had gained 25 pounds (11.34 Kg.) in the previous three years. Her weight was 156 pounds (70.76 Kg.); her height, 5 feet and $\frac{1}{2}$ inch (153.6 cm).

As she came into the office she presented the same type of dyspnea seen in cases 1 and 2, and she was obliged to rest a few moments before she could give her history. Slight exertion made her short of breath. This was more marked after eating, and she had found that she felt much better when she sat down for an hour after eating. Her dyspnea was even more marked on lying down. If she did not have three pillows when she retired, her breathing would become difficult even though it was normal while she was sitting up.

Her digestive symptoms had never been pronounced. As a young woman she had attacks of "nervous indigestion" every spring and fall when she was overtired. These attacks consisted of regurgitating part of the meal or of vomiting the entire

meal when she overloaded her stomach. There was no nausea, gas or any other symptom of indigestion. She had been free from these attacks for years, as she had learned not to "overeat."

Careful examination failed to show any cause for her dyspnea other than obesity. Reduction in weight relieved her dyspnea when she was lying down, but otherwise there was no change. She has been seen at frequent times since, her dyspnea has gradually increased, and of late there has been some palpitation.

She was examined roentgenologically with the possibility of thoracic stomach in mind. The entire stomach was above the diaphragm, and the esophagus was seen by fluoroscope to enter the stomach at the level of the eighth thoracic vertebra.

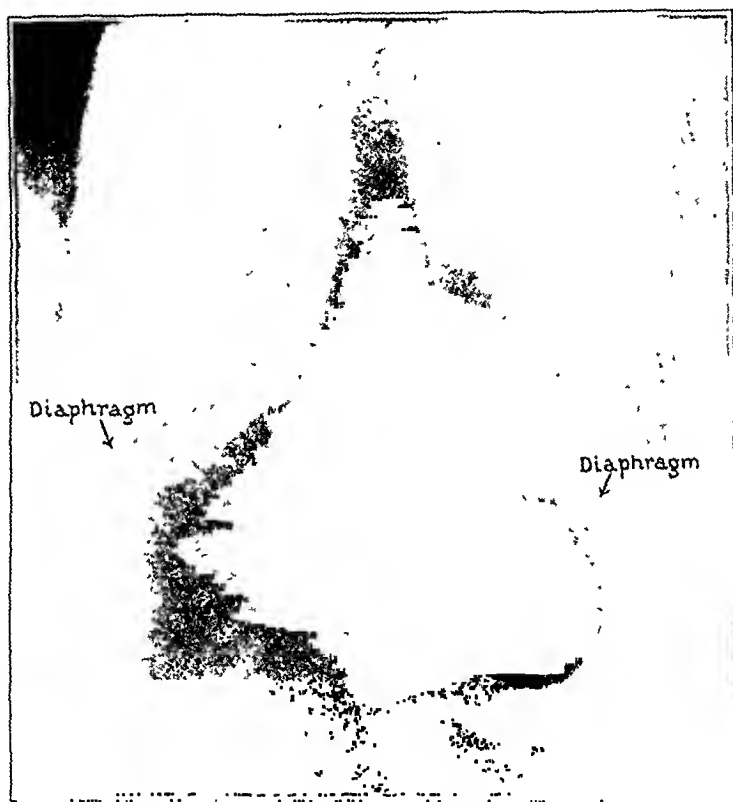


Fig. 4.—This roentgenogram shows a typical thoracic stomach which up to the time of our investigation had been diagnosed as "hernia of the stomach through the esophageal opening of the diaphragm." The foreshortened esophagus is demonstrated beyond question, and in this case about two thirds of the stomach is above the diaphragm.

In these three cases the greater part of the stomach was above the diaphragm, and we shall from now on refer to such cases as cases of the first type. In the next two cases that we shall report the greater part of the stomach was below the diaphragm, and we shall refer to such cases as cases of the second type. This distinction is made as the clinical symptoms vary according as the bulk of the meal is above or below the diaphragm.

We were unfortunate in being unable to obtain a roentgenogram in any of our three cases showing the foreshortened esophagus. A roentgenogram from a typical case is shown which clearly reveals the fore-

shortened esophagus with about two thirds of the stomach above the diaphragm (fig. 4). This is a fairly recent case which was diagnosed by Morrison⁸ as "hernia of the stomach through the esophageal opening, of the short esophageal type."

The next two cases that we report are cases of the second type. In both instances the diagnosis of thoracic stomach was suspected, and the patients were referred for special examination as to the length of the esophagus.



Fig. 5 (case 4) —This roentgenogram demonstrates the foreshortened esophagus that just fails to reach the esophageal opening of the diaphragm; a small portion of the fundus of the stomach is seen above the diaphragm.

CASE 4—A woman was first seen in 1923 at the age of 48. Her weight was 155 pounds (70.30 Kg.); her height, 5 feet and 1½ inches (156.2 cm.). For nearly ten years she had complained of marked hyperacidity with gas and burning in the stomach, that had resisted all treatment. With frequent small meals and alkalis she was comfortable, but the moment she broke her diet or gave up taking

8. Morrison, L. B : Diaphragmatic Hernia of Fundus of Stomach Through Esophageal Hiatus, *J. A. M. A.* **84**:161 (Jan. 17) 1925.

alkali the symptoms recurred. During this period a complete roentgen examination was made twice; the first time nothing abnormal was found, and the second time a duodenal ulcer of suspicious character was reported. The latter time the results of the physical examination were negative aside from the fact that she had a tenderness over the gallbladder. A fractional test meal showed a marked hyperacidity. There was no blood in the stomach contents or in the stools. Another complete gastro-enteric roentgen examination, including the gallbladder, was made in 1923 and was reported to give negative results. Previous clinical diagnoses had been made of ulcer of the stomach and the duodenum and of disease of the gallbladder. Operation had been advised but refused. We were unable to make a satisfactory diagnosis, but we put her on the regular treatment for ulcer, with relief of her symptoms. Whenever she overstepped her diet or gave up the alkalis the symptoms promptly returned. She complained of dyspnea, but only on exertion and we did not associate this with her digestive symptoms.

Reduction in weight to 135 pounds (61.13 Kg.) relieved her dyspnea but did not in any way alter her digestive symptoms. Soon after this a progressive chronic polyarthritis developed, and she was under the care of an orthopedic surgeon who gave her a diet for arthritis.

In October, 1932, she returned, saying that the diet she was following for her arthritis had greatly aggravated her digestive symptoms which she now described as "coals of fire in her stomach." The only thing that relieved her was soda, and she had taken "tons of it and was afraid to continue." During this interval she had been thoroughly examined roentgenologically, again with negative results. Dyspnea had not been a prominent symptom. At this time the results of a physical examination were negative aside from the fact that there was acute tenderness with a definite muscular rigidity over the gallbladder.

In view of the fact that her symptoms were so persistent and that repeated roentgen examinations had failed to demonstrate any abnormality of the gastro-enteric tract, we suspected the possibility of thoracic stomach or hernia of the stomach through the diaphragm. We sent the patient to the New England Deaconess Hospital the following day with a special request for an examination of the esophagus, stomach and gallbladder. The gallbladder was normal. It was found that the esophagus fell just short of reaching the diaphragm and that a very small portion of the fundus of the stomach was in the thorax.

CASE 5.—A woman was seen first in 1920 when she was 57 years of age. Her height was 5 feet and 1 inch; her weight, 139 pounds (63.04 Kg.). Six months before she weighed 150 pounds (68.04 Kg.). She had reduced her weight at the advice of her physician. Reduction in weight, however, did not relieve her symptoms.

For one year she had complained of symptoms of hyperacidity which, while slight at first, had gradually increased in severity up to the point where she was distressed all of the time. According to her past history she had never presented any digestive symptoms before this occurrence. In spite of treatment she had grown progressively worse. She complained of dyspnea on exertion; this was more marked after eating. However, it was not a disturbing symptom.

On physical examination she showed a moderate degree of thickening of the external arteries; the heart was slightly enlarged to the left; there was a mitral systolic murmur transmitted to the axilla; the second aortic sound was accentuated; the specific gravity of the urine was 1.010; there was the slightest possible trace of albumin, and casts were found in the urine. The blood pressure was 150 systolic and 100 diastolic. There was definite evidence of disease of the heart and kidneys.

There was definite tenderness over the gallbladder but no muscular rigidity. A fractional test meal showed a moderate hyperacidity. There was no blood in the stomach contents or in the stools. A complete gastro-enteric roentgen examination was made with the diagnosis of a "possible duodenal ulcer." With the usual treatment for ulcer the symptoms were relieved, but when she deviated from this regimen, the symptoms returned.

In 1921, after an indiscretion in diet, she had an attack of acute abdominal pain with tenderness in the region of the gallbladder. There was no temperature, nausea, vomiting or jaundice. Her local physician made a diagnosis of gallstones and advised operation. This attack lasted three days. She was not operated on.

After this she was more careful of her diet, and although she was always conscious of "indigestion" she was fairly comfortable.

In 1930, after another "hearty meal" she had a second attack, similar to the previous one. Since then she has been very careful not to overeat, and there has been no recurrence of these attacks.

Since this time dyspnea and palpitation have been the distressing symptoms. The blood pressure had gradually increased until at the time of this examination it was 200 systolic and 120 diastolic. Dyspnea and substernal pressure after eating, and numbness down the left arm, also after eating, were the predominating symptoms. She definitely associated these symptoms with overeating. Physical examination of the heart failed to show sufficient change to explain all the symptoms; she was sent to the hospital on Dec. 15, 1932, and the usual roentgen examination was requested. Roentgenograms showed an esophagus that just failed to reach the esophageal opening of the diaphragm, and a small portion of the fundus of the stomach was seen above the diaphragm. In certain aspects this case differs clinically from the other four cases, as the patient had definite cardio-renal disease.

FREQUENCY OF THORACIC STOMACH

Including our five cases only twelve cases have been reported in the literature. This seems to indicate that the condition is rare. We believe, however, that the condition is a common one which has been overlooked, as the presence of the stomach, or a part of the stomach, in the thoracic cavity has been considered to be hernia of the stomach through the esophageal opening of the diaphragm. We are referring, of course, to the congenital cases and not to the traumatic cases which belong in a class by themselves.

This is a matter of surprise as the literature on hernia of the diaphragm⁹ is quite complete. As far back as medical records go, cases

9. Richards, L. G.: Nontraumatic Hernia of Diaphragm, *Ann. Otol., Rhin. & Laryng.* **32**:1145 (Dec.) 1923. Bowditch, H. I.: *Treatise on Diaphragmatic Hernia*, Buffalo, Jewett, Thomas & Co., 1853. Nothnagel, H.: *Specielle Pathologie und Therapie*, Vienna, A. Hölder, 1894, Supp. no. 1-6-G-178. Ritvo, M.: Hernia of Stomach Through Esophageal Orifice of Diaphragm, *J. A. M. A.* **94**:15 (Jan. 4) 1930. Truesdale, P. E.: Diaphragmatic Hernia: Its Clinical Aspect from Trauma in Children, *J. A. M. A.* **77**:993 (Sept. 24) 1921; *New England J. Med.* **207**:385, 1932.

have been reported. We can divide these reports into two distinct periods depending on the advent of roentgen examination.

Before the discovery of the roentgen ray the cases were found by the pathologist, the anatomist and rarely by the surgeon. It was considered a rare condition. The herniated portion was described as going through certain weak spots of the diaphragm resulting from developmental errors. If the foreshortened esophagus was discovered, its significance was overlooked.

With the improvement of roentgen technic, during routine gastroenteric examinations a portion of the stomach could be found above the diaphragm in persons in whom the condition was unsuspected. This has stimulated further investigations, and today all roentgenologists agree that hernia of the stomach is a common condition.

Morrison⁸ and Healy¹⁰ deserve the credit for demonstrating its frequency. They discovered this by accident. In 1922 they began a special study of the fundus of the stomach with the idea of determining some method whereby an early diagnosis of a malignant condition of the cardia could be made.

In order to get a clear picture of the fundus they "filled" the stomach with barium sulphate, put the patients in certain positions (supine, Trendelenburg, etc.) and then applied pressure over the epigastrium. During these special examinations they found that a portion of the fundus was "herniated" through the diaphragm in twelve cases. In 1925 Morrison⁸ reported a total of forty-two cases of this type, and six months later Healy¹⁰ brought the total up to fifty-three. These findings stimulated other roentgenologists to make similar examinations, with the result that many cases are now to be found in the literature.

Morrison⁸ and Healy¹⁰ classified these cases as hernia of the stomach through the esophageal opening of the diaphragm, and designated the cases in which a considerable portion of the stomach was in the thoracic cavity as "hernia of the short esophageal type."

From what we can find in the literature, this classification has been accepted by all of the roentgenologists with the exception of LeWald,⁹ who recognized thoracic stomach.

We question the frequency of the occurrence of hernia through the esophageal opening. We admit its possibility, but we are certain that the roentgenologist has overlooked many cases of thoracic stomach and cases of true hernia of the diaphragm.

In order to support this contention it is necessary to review briefly the embryology of the organs concerned.

10. Healy, T. B.: Symptoms Observed in 53 Cases of Non-Traumatic Diaphragmatic Hernia, *Am. J. Roentgenol.* **13**:266, 1925.

EMBRYOLOGY OF THE FOREGUT AND OF THE DIAPHRAGM

Unfortunately the embryology of the foregut and of the diaphragm have not been thoroughly worked out, but enough has been done to make the occurrence of the conditions described explainable.

The primitive gut starts as a straight tube which promptly becomes differentiated into a foregut, a midgut and a hindgut. From the foregut, which is relatively short, develop the esophagus and the stomach, the stomach appearing as a dilatation of the hind portion of the foregut. From the esophageal portion of the foregut the esophagus and the trachea develop. In front of this portion is the pharynx. This separation of the esophagus and the trachea begins in the early part of the third week of the embryo. The first indication is a longitudinal groove on the inner surface of its ventral wall. At this point the esophagus stops growing lengthwise, but begins to widen in order to form two tubes, the future trachea and the esophagus of the same caliber as the original esophagus. As this change takes place there is a temporary atresia of the esophagus in order to protect the lung, which is developing from this primitive trachea, from the possible inhalation of extraneous matters. By the beginning of the fourth week this longitudinal groove has deepened to complete separation, and two tubes are formed, connected only at the pharyngeal opening. The tube with the blind ending is the future trachea from which the lungs develop.

Once this separation is complete, under normal conditions, the atresia of the esophagus is relieved, and the esophagus resumes its growth. Three developmental errors may, however, occur at this point: 1. The atresia may not be relieved, giving rise to congenital atresia of the esophagus. 2. Widening of the esophagus may advance to an abnormal degree, giving rise to an abnormally wide esophagus. 3. The esophagus may fail to resume its growth, giving rise to thoracic stomach. In other cases growth of the esophagus is resumed, but, for some reason which we cannot explain, fails to reach its normal length. In some cases of thoracic stomach the esophagus appears to be abnormally wide, and it is suggested that this may be one reason for the occurrence of the anomaly, as increase in width would probably result in foreshortening.

We are obliged to consider the possibility that the diaphragm in its descent goes to an abnormally low position, leaving the esophagus behind. We can find no mention of such an occurrence, however.

Bailey,¹ in discussing the cause, thought that the anlage of the stomach was too far forward on the foregut. No other theories have been advanced.

True hernia of the diaphragm results from improper fusion of its various layers during its development, the most common fault being

found in an improper closure of the pleuroperitoneal canal. In true hernia the esophagus goes through the esophageal opening normally, and the herniating fundus passes up through one of these weak points.

These two definite conditions being presented, there remains a third possibility to be considered, namely, "hernia of the stomach through the esophageal opening of the diaphragm." Strictly speaking there is no esophageal opening of the diaphragm. As the diaphragm develops, two strong muscular bands, attached to the crura, develop. These two muscles closely surround the esophagus, leaving no opening. Any congenital error of these two muscles gives symptoms at birth, or soon after, and not late in life.

Morrison⁸ and Healy¹⁰ admitted this fact but claimed that with long-continued "indirect pressure," such as obesity, long-continued cough or other strains, a portion of the fundus is herniated and dilates these muscles, causing hernia.

It is evident that muscles of this character could not lose their elasticity unless the pressure was continuous; consequently such dilation does not seem probable. If, as we believe, these are cases of thoracic stomach, the esophageal opening would from necessity be larger than normal, owing to the fact that the portion of the stomach passing through the opening has a caliber larger than that of the esophagus, and the muscles in approximating the viscus would present a wider space. Furthermore it is difficult to understand the mechanics of "indirect pressure." No one would eat a meal comparable to the amount of barium sulphate that has to be given to demonstrate the hernia by roentgen examination.

In the two cases of the second type and in other cases which we have not reported it is demonstrated that, as the stomach begins to empty, enough barium sulphate remains in the herniated portion to show that it is still above the diaphragm and to make it appear to be fixed there. Morrison⁸ stated that this type of hernia is easily overlooked during a routine gastro-enteric examination, on account of the fact that as soon as the stomach begins to empty there is a spontaneous reduction of the hernia. In both of the two cases, however, this was shown not to be the fact. In both, as the stomach began to empty, enough barium sulphate remained in the "herniated portion" to demonstrate without question that the herniated portion was fixed above the diaphragm and that reduction did not occur.

We believe that this herniated portion of the stomach is fixed in a position above the diaphragm by the foreshortened esophagus, and we can find no roentgen evidence to contradict this opinion. Roentgenologists, with the exception of LeWald,³ have failed to recognize thoracic stomach and, in consequence, have paid little or no attention to the length of the esophagus.

If we are correct in our supposition, it is easy to understand why this herniated portion is so easily overlooked during the ordinary roentgen examination of the gastro-enteric tract and why such unusual methods as those described by Morrison^s are required to fill the herniated portion.

Morrison^s observed that "in nearly all hernia cases the esophagus seems a trifle enlarged." This supports our theory, already mentioned, that one reason why the esophagus fails to reach the diaphragm is that its caliber is abnormally enlarged.

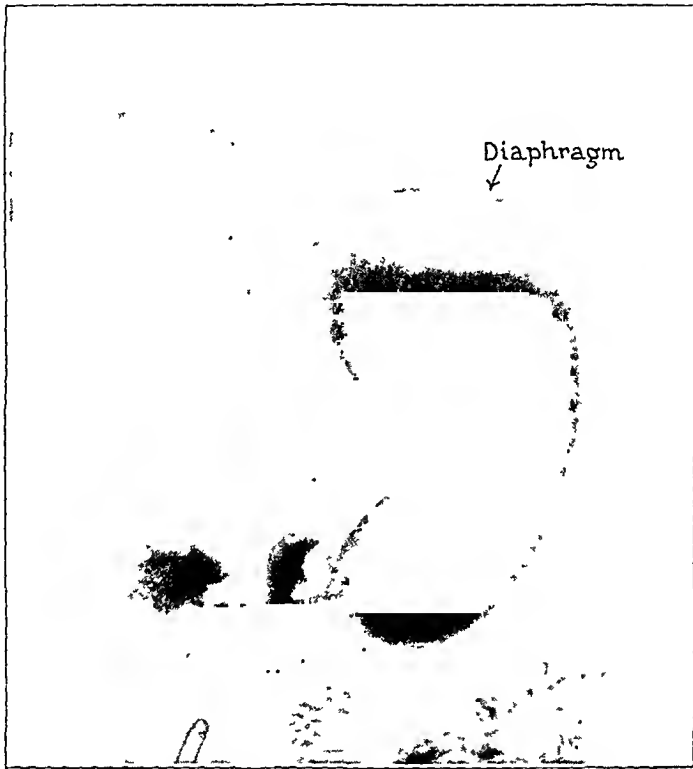


Fig. 6 (case 5) —The stomach is beginning to empty, yet enough barium sulphate remains in the small portion of the stomach above the diaphragm to demonstrate the fact that this is not a case of hernia through the esophageal opening. It is evident that the short esophagus is holding this small portion of the fundus above the diaphragm. From this roentgenogram it is evident that by fluoroscopic examination the mass of barium sulphate may appear to be reduced, but it is to be remembered that the fluoroscope shows the mass of barium alone and cannot demonstrate the position of the stomach itself. This figure suggests that any tension on the stomach is in the downward direction, yet the small portion of the stomach still remains above the diaphragm.

Some of Morrison's^s observations require further comment. He stated that small hernias are difficult to demonstrate in a roentgenogram. With the fluoroscope, however, the small herniated portion can be seen passing up and down through the esophageal opening. Fluoroscopic

observations are limited largely to the activity of the mass of barium sulphate and we should expect that with a full stomach this fixed portion of the stomach would fill and empty with normal peristalsis. There is no evidence, however, that the stomach itself moves up and down through the opening.

We are unable at the present time to give definite statistics as to the frequency of thoracic stomach. It is interesting, however, to note that a diagnosis of hernia of the stomach through the esophageal opening of the diaphragm has been made at the New England Deaconess Hospital in forty-seven cases. The length of the esophagus was undetermined in twenty-two cases. In twenty-one cases a short esophagus was demonstrated, and in four cases the esophagus was seen to pass through the esophageal opening of the diaphragm. We conclude that twenty-one cases were cases of thoracic stomach, and four, cases of true hernia of the diaphragm. We realize that this is a comparatively small number of cases, but from a review of the literature on "hernia of the diaphragm" we believe that they are highly significant.

SYMPTOMS OF THORACIC STOMACH

Bailey's¹ patient lived to be 77 years of age without any symptoms referable to the condition. As the condition is congenital this is not a matter of surprise. We believe that many persons have lived their natural lifetimes without the condition being suspected.

When symptoms occur, they are the result of two distinct mechanisms: (1) interference with normal peristalsis of the gastro-intestinal tract and (2) embarrassment of the thoracic organs.

Symptoms may occur at birth, in which event there must be some other congenital disturbance, the most probable one being some interference with the normal rotation of the stomach. It is even possible that the different types of stomach described in "hernia" are the result of abnormal disturbances in the rotation of the stomach as a result of the short esophagus.

Furthermore, it is probable that with developmental errors of the esophagus other developmental errors of the digestive tract occur. Attention has already been called to the occurrence of the abnormally wide esophagus. In the forty-seven cases observed at the New England Deaconess Hospital, two showed a diverticulum of the esophagus; one, a diverticulum of the duodenum, and five, a diverticulosis of the colon. In one case there was an eventration of the diaphragm. In one doubtful case reported as one of "hernia" there was a congenital atresia of the duodenum.

In many of these cases giving rise to symptoms early in life the symptoms do not occur until the child changes from a milk diet to a general one.

If symptoms do not occur during the first five years of life they do not, as a rule, occur until early or late adult life. Just what occurs to interfere with normal peristalsis at this time is not quite clear. In many instances it is certain that complications occur, especially duodenal ulcer, which appears to be not infrequent in thoracic stomach. In others it is possible that the lack of muscular tone is responsible.

In the cases of the first type it would appear that symptoms, as a rule, do not appear until late in life, when the lung loses its elasticity or the myocardium begins to degenerate. The symptoms may be divided into two distinct groups: 1. Cardiorespiratory: These symptoms predominate in the first type of case, in which the bulk of the stomach is above the diaphragm. 2. Gastro-intestinal: These symptoms predominate in the second type of case, in which the bulk of the stomach is below the diaphragm.

Dyspnea.—Dyspnea is a characteristic symptom in the first type of case. With ordinary activity, such as walking a short distance or doing the easiest kind of work, such as dusting, the patients begin to "pant" as if they had been running. If they sit down for a few minutes, the breathing becomes normal again. During this period, they do not even feel like talking. If the heart is normal, there is no particular increase in pulse rate. This dyspnea is more marked immediately after eating. When the stomach is empty, activity may not give rise to dyspnea. If the patient lies down immediately after eating, the dyspnea is often more pronounced. If there is evidence of myocarditis, an increased pulse rate may be observed.

In the second type of case dyspnea is not a symptom unless there is some definite interference with the action of the diaphragm. In true hernia of the diaphragm dyspnea is a frequent symptom, and in cases of thoracic stomach of the second type with ulcer, dyspnea may be a symptom.

Morrison⁸ reported that in some of his patients who were operated on, the margins of the esophageal opening were thickened, and the stomach wall showed more or less dense cicatricial-like thickening over the portion that had become herniated, which indicated some inflammatory process. The roentgenologist demonstrated ulcer in some of these cases, but in our first case reported the occurrence of the ulcer was entirely overlooked in the roentgenogram. One can only conclude that the roentgenologist is definitely limited in his ability to make a positive diagnosis in the cases showing abnormally developed stomachs.

Cardiac Symptoms.—In the first type of case a sense of substernal fulness is common if the person overeats. LeWald's patient said "she could feel her stomach in her chest" after overeating. In all of the

patients who have complained of this sensation immediate relief has been obtained by regurgitation or vomiting. In only one of the twelve cases reported were there symptoms suggestive of angina.

Angina Pectoris.—Symptoms of angina pectoris are by no means uncommon in cases of true hernia of the diaphragm. In thoracic stomach, however, these symptoms never occur except in the event of complications. In one of our cases a diagnosis of angina and acute indigestion had been made, but in this case the colon had herniated through the esophageal opening. It is probable that in cases of ulcer in the region of the esophageal opening with adhesions symptoms of angina may occur. It is probable that any symptom of angina may suggest the herniation of some other abdominal organ.

Palpitation.—In the first type of case palpitation occurs only when myocardial changes are present or when an ulcer at the esophageal opening interferes with normal peristalsis. In true hernia palpitation is frequently a distressing symptom. When it occurs in thoracic stomach we must assume that the stomach has become adherent to the muscles of the esophageal opening, as a result of ulcer.

Gastro-Intestinal Symptoms.—From the standpoint of the patient gastro-intestinal symptoms are practically negligible in the first type of case; yet, clinically, they are suggestive. They are essentially mechanical, and occur only when the patient overeats.

The usual story is that with the ingestion of too much food, too rich foods or too highly spiced foods or the ingestion of too much liquid with the meal there is a sensation of fulness, and a part of the meal, occasionally the entire meal, is regurgitated. This occurs without nausea, gas or any other symptom of indigestion, and this regurgitation immediately relieves the sensation of pressure. When real symptoms of indigestion occur in this type of case, it suggests that some complication, such as ulcer, is present.

In the second type of case regurgitation is rare, but may occur. In one case, in which the small portion of the fundus was demonstrated as being fixed above the diaphragm, the patient complained of a sensation of fulness after a few mouthfuls of food, evidently after the intake of enough food to fill this "herniated" portion. Occasionally regurgitation would occur, but as a rule if the patient waited a few minutes, she could finish the meal without discomfort. Evidently the pressure of this small amount of food dilated the constricting opening and permitted the food to pass through without further discomfort.

The real digestive symptoms in this type of case are those of a persistent, often severe hyperacidity.

In the majority of the cases which have been overlooked during the roentgen examination the diagnosis has been disease of the gallbladder.

ulcer of the duodenum, ulcer of the stomach or appendicitis. Many of the patients have been operated on with negative results. One unfortunate woman was operated on three times—once for appendicitis, once for gallstones and once for adhesions—before the “hernia” was demonstrated. In several cases gallstones have been demonstrated and operations have been performed without relief of symptoms, and later examination has shown the presence of “hernia.”

Acidity.—In our two cases a fractional test meal showed a marked hyperacidity. In both cases the stomach contents and the stools were negative for blood. In both of these cases, as in cases of ulcer, there were periods of remission, but at no time were the patients free from symptoms.

One suggestive feature of the acidity, which may be characteristic, is the fact that if a hearty meal is eaten, the acidity is almost immediate; if a small meal is taken, the acidity does not appear until from one to four hours after eating.

Abdominal Pain.—Abdominal pain has been observed only in cases of the second type and in these only during the attacks of severe gastric distress. Pain, tenderness and muscular rigidity in the epigastrium and in the region of the gallbladder have been observed during these severe attacks.

Dysphagia.—Dysphagia is a frequent and distressing symptom in true hernia of the diaphragm. It is not a symptom of thoracic stomach. It is not reported to be a common symptom of “hernia through the esophageal opening of the esophagus” as we should expect it to be.

Nausea and Vomiting.—Nausea and vomiting may occur during the acute attacks of hyperacidity in the second type of case, but, as a rule, the occurrence of these symptoms would suggest some complication, such as duodenal ulcer.

Gas.—The presence of gas is unusual in the first but common in the second type of cases. There is nothing characteristic about it, however. In true hernia of the diaphragm gas is often a distressing symptom, and its occurrence aids in the clinical differentiation of thoracic stomach and true hernia.

Constipation.—Constipation is frequently referred to in reported cases of hernia of the diaphragm, but, so far as we can determine, it has no particular bearing on the condition, unless the intestines are herniated and are to be found in the thorax.

Other Symptoms.—We have attempted to confine our observations to the relatively few cases which we are certain are cases of thoracic

stomach. In the literature of diaphragmatic hernia, however, many distressing symptoms are reported which have led to the diagnoses of asthma, pulmonary tuberculosis, myocarditis, angina pectoris and practically all of the abdominal diseases.

From the observations that we have already made it is possible to understand why such diagnoses would be made. There remains, however, one observation which should be commented on, namely, the occurrence of anemia in "hernia" of the diaphragm.

In the most recent report calling attention to this finding, Weitzen⁶ entitled his article "Diaphragmatic Hernia with Severe Anaemia." Our first case presented a moderate anemia that did not respond to treatment. At postmortem examination we found that the patient had an ulcer of the duodenum that was overlooked in roentgen examination and that was probably responsible for her anemia. Morrison⁸ reported cases in which the patients vomited blood but failed to show any ulcer. We believe that the roentgenologist has definite limitations in this field of diagnosis in cases of "hernia of the diaphragm." It is our opinion that anemia is no more frequent in cases of "hernia" than in the ordinary course of life, and that its occurrence suggests ulcer.

TREATMENT

It can be definitely stated that thoracic stomach is a problem that belongs to the field of the internist and not to that of the surgeon, for, because of the short esophagus, the abnormality cannot be corrected. Medical treatment, from necessity, has its limitations, but it can at least prevent unnecessary operations and unnecessary medication such as treatment with digitalis. It can do much more than this, since it is possible to keep the patient in comparative comfort and perhaps to prevent complications. In order to do this it is necessary to have the complete cooperation of the patient just as in all incurable conditions, such as diabetes and tuberculosis.

The diagnosis must be definitely made and the condition fully explained to the patient.

For the most part the treatment is dietary. The first essential is to avoid overeating. Frequent small meals must be taken. Rich foods and highly spiced foods must be avoided. Fluids with meals should be restricted. A bland diet such as that recommended by Alvarez should be prescribed. Meat should be eaten once a day at least. The clothing about the thorax and abdomen should be loose. It is desirable to maintain the patient at his normal weight. The upright position should be maintained for at least one hour after the principal meals of the day.

Patients presenting the symptoms of hyperacidity should be treated as if they had ulcer of the stomach or duodenum, regardless of whether the roentgen findings are positive or negative as to the occurrence of ulcer.

If, under these conditions, the patient cannot be made comfortable, or if distressing symptoms occur, some complication should be suspected.

CONCLUSIONS

Thoracic stomach is a definite clinical entity belonging in the field of the internist. We believe the condition to be a fairly common one. Its seeming rarity is due to the fact that cases, especially of the second type, have been overlooked by the roentgenologist and probably by the pathologist.

We believe that the clinical symptoms are characteristic enough to permit a tentative diagnosis.

Dyspnea of the type described, occurring in the latter part of life, suggests thoracic stomach.

Unmitigated gastro-intestinal symptoms with negative routine roentgen findings should make one suspicious of thoracic stomach.

One must, of course, depend on the roentgenologist for the final diagnosis, and this necessitates a routine determination of the length of the esophagus in all gastro-enteric examinations.

The occurrence of ulcer in thoracic stomach cannot always be demonstrated by roentgenograms.

We hope that this report will stimulate the anatomist and the pathologist to make more careful observations of the organs involved, giving special attention to cases of the second type.

We are at the present time engaged in a complete review of "hernia of the diaphragm" and a more detailed report will be made later.

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CHRONIC IDIOPATHIC STEATORRHEA

ROENTGENOLOGIC OBSERVATIONS

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The first hint of a clinical syndrome in which diarrhea was associated with metabolic disorders appeared in Trousseau's¹ celebrated lecture on tetany. It is now well recognized that certain types of fatty diarrhea may be associated with serious depletion of calcium and tetany. These clinical syndromes are described under the names of "nontropical sprue," "idiopathic steatorrhea," "Gee's disease," "Gee-Herter disease," "adult celiac disease," "intestinal lipodystrophia" and various other names. If one may judge from current reports in the literature and from our experience, this condition is probably considerably more common than is generally believed.

The literature on this disorder has been completely reviewed in recent reports by Linder and Harris,² Bauer and Marble,³ Bennett, Hunter and Vaughan,⁴ physicians of the Mayo Clinic, and numerous other authors. The clinical picture, as established by previous reports, is that of fatty diarrhea with associated changes in the metabolism of calcium and phosphorus, the extent of these last mentioned phenomena depending on the duration and the severity of the diarrhea. The condition closely simulates tropical sprue, differing from it chiefly in the fact that its victims have resided in temperate climates. It usually pursues a chronic course with exacerbations and remissions, and in certain cases it appears to represent a long-standing deficiency in the

From the Division of Medicine and the Section of Roentgenology, the Mayo Clinic.

1. Trousseau, Armand: Lectures on Clinical Medicine, London, The New Sydenham Society, 1868.

2. Linder, G. C., and Harris, C. F.: Calcium and Phosphorus Metabolism in Chronic Diarrhoea with Tetany, *Quart. J. Med.* **23**:195 (Jan.) 1929.

3. Bauer, Walter, and Marble, Alexander: Studies on the Mode of Action of Irradiated Ergosterol: II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases, *J. Clin. Investigation* **11**: 21 (Jan.) 1932.

4. Bennett, T. I.; Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease): Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, *Quart. J. Med.* **1**:609 (Oct.) 1932.

digestion and absorption of fat and other substances which began in early life and continued into maturity; for this reason it has been referred to as adult celiac disease. It appears to be somewhat more common among females, but cases of marked severity have been reported as affecting persons of both sexes. The principal complaint is usually that of long-continued diarrhea, which may be intermittent or continuous. In most instances, two or more bulky, foul, grayish stools are passed daily. Exacerbations of the diarrhea are not uncommon, and in some of our cases appear to have been more common in the spring. Each episode of diarrhea may be associated with increasing loss of weight, flatulent indigestion and attacks of active tetany. Loss of weight is usually extreme, and with it there is a corresponding degree of malaise and physical debility. The appetite is often capricious, and there may be marked anorexia. There is often a history of latent tetany of long standing, with muscular cramps and paresthesia, and in certain instances this is the most conspicuous feature of the disease, antedating the diarrhea by considerable periods. A history of glossitis is common. Pains in the bones and joints are not infrequent, especially in the more advanced cases, and may represent the earliest symptoms of depletion of the skeletal reserve of calcium.

On physical examination the patients are usually markedly emaciated and dehydrated. Some are of constitutionally substandard types, and in at least three of our cases there were evidences of serious growth defects which obviously dated back to early life. Marked pallor is commonly noted. Often there is active glossitis, as well as areas of atrophy on the tongue. Hypothermia, lowered blood pressure and a slow pulse are not uncommon. The abdomen is usually distended and is in sharp contrast to the general emaciation, a feature which numerous writers have noted. Kyphosis, pelvic contractures and other signs of osteomalacia may be apparent. The deep reflexes may be absent, but there are rarely sufficient neurologic findings to suggest the diagnosis of subacute combined degeneration of the spinal cord. Peripheral neuritis and eruptions resembling pellagra have been described. In two of our cases, definite edema of the nutritional type was encountered, and this feature has also been noted by other observers.

Laboratory data are of definite diagnostic value, and the abnormalities of metabolism of calcium and phosphorus may be regarded as sufficient to distinguish this disorder from other conditions associated with tetany, as has been shown by Aub and his associates,⁵ and by

5. Aub, J. C.; Albright, Fuller; Bauer, Walter, and Rosemeisl, Elsie: Studies of Calcium and Phosphorus Metabolism: IV. In Hypoparathyroidism and Chronic Steatorrhea with Tetany with Special Consideration of the Therapeutic Effect of Thyroid, *J. Clin. Investigation* **11**:211 (Jan.) 1932.

Bauer and Marble. The concentration of calcium and of phosphorus in the blood are both reduced; the urinary excretion of calcium is also low, but the fecal excretion of this substance is increased. There is also marked increase in the urinary excretion of phosphorus. The reduced value for serum phosphorus serves of itself to distinguish this condition from true parathyroid tetany, in which the reverse is the rule. Marked secondary anemia is usually present, or blood smears may reveal well developed macrocytosis. In some of our cases, however, small and irregular red blood cells predominated in the smears. Complete achylia is not particularly common, but lowered gastric acidity has been reported by numerous observers. The basal metabolic rate may be considerably reduced, although in many cases the muscular hypertonicity associated with latent tetany may interfere with obtaining a true basal reading. In the stools there is excess of neutral fat and fatty acids, and experiments in metabolism have shown that the loss of fat from this source may be considerable. The values for serum protein are often reduced to a level at which any excess of intake of fluid will result in the development of edema.

Roentgenologic observations reported in the literature concerning this condition have been limited to the gastro-intestinal tract and the skeletal system. Osteoporosis and osteomalacia have been noted frequently. Dilatation and redundancy of the colon have been commonly observed, but abnormalities of the stomach or small intestine have not been noted except in the case described by Radl and Fallon.⁶ These authors noted marked narrowing of the second and third parts of the duodenum, suggesting ulceration with periduodenal adhesions. An ulcer was also observed in the first portion of the duodenum, producing gastric retention for which gastro-enterostomy was performed. It was suggested that the narrowing of the duodenum had interfered with the normal passage of pancreatic secretion.

The cases reported in this paper were observed at the Mayo Clinic. Significant data on all cases are given in the accompanying table. Clinical features of the first five cases have been reported previously and will not be repeated here. However, special attention is given to roentgenologic observations in all cases in which information was available. Similar roentgenologic findings have not been reported heretofore.

In all of the seven cases (except case 2) roentgenologic studies of the gastro-intestinal tract were made. In cases 1 and 3 the results were negative. In the remaining four cases roentgenologic examination revealed definite abnormalities in the contour and motility of the small intestine.

6. Radl, R. B., and Fallon, Madelein: Nontropical Sprue with Duodenal Involvement and Tetany, *Arch. Int. Med.* **50**:595 (Oct.) 1932.

Summary of Cases

Case	Yrs.	Age	Sex	Diarrhea		Tetany		Gloss- itis	Post- men- opause	Approx- imate Loss of Weight, Lbs.	Hemo- globin, per Cent	Eryth- ro- cytes, Millions	Gastric Acidity, Free and Total*	Serum		Basal Meta- bolic Rate, per Cent	Osteo- porosis	Comment
				Dura- tion	Sever- ity, Grade	Dura- tion	Sever- ity, Grade							Calc- ium, Mg. per 100 Cc.	Phos- phates, Mg. per 100 Cc.			
1	32	F		1. Mc- long	2	7	2	+	+	45	51	3.60	40/56	6.3 11.3	4.4 6.6	+12	None	Under observation 8 years; in good health at time of writing; normal pregnancy 2 years before time of writing; taking calcium lactate and cod liver oil
2	33	F		Inter- mittent, 6 to 7 years	1	5	2	0	+	40	54	4.09	18/38	6.3 8.2	2.3 4.5	+ 8	Marked	Somewhat relieved by high vitamin intake and calcium; died 3 years after treatment begun from intercurrent infection
3	51	F		6 to 7 years inter- mittent, 2 to 4	2	2	3	0	Post- men- opause	20	62	3.91	0/10	4.9 7.7	2.1 4.6	Not deter- mined	None	Tetany controlled by parathyroid extract-Collip but diarrhea intractable; patient left hospital against advice
4	47	F		20 years	2	20	2	+	+	25	38	3.71	0/10	6.3 11.6	4.0 4.1	+17	None	Tetany controlled by parathyroid extract-Collip and high vitamin diet; finally "cured" by viosterol; gained 23 pounds (10.4 Kg.); well 2 years after treatment began
5	47	M		1 year	3	10	1	+	..	50	75	4.89	44/56	6.8 8.6	2.9 3.9	-15	None	Relieved by viosterol and calcium lactate and high protein diet; had definite nutritional edema at onset; well several months after treatment began
6	41	M		6 months	3	0	0	+	..	26	70	3.42	8/23	8.0 10.5	2.2 3.4	- 4	Slight	Much benefited originally by viosterol and high protein diet; easily upset by dietary error
7	45	F		8 months	3	0	0	+	+	22	67	3.82	46/58	7.8 9.0	2.8 3.0	- 6	None	Benefited by viosterol but very low tolerance for fat; one severe episode of diarrhea in month before time of writing

* In terms of cubic centimeters of tenth-normal sodium hydroxide required to produce end-point in 100 cc. of strained gastric content.

† Method of Kramer and Tisdall.

‡ Method of Fiske and Subarow.

REPORT OF CASES

CASES 1, 2 and 3.—Case 1 has been reported by Snell and Habein;⁷ case 2, by Constam and Partch,⁸ and case 3, by Snell.⁹

CASE 4.—The clinical features of this case have been reported by Snell.

Roentgenologic examination on Feb. 7, 1930, revealed the deformity of an ulcer in the first portion of the duodenum. There was some dilatation of the second portion of the duodenum and some smoothing out of the usual serrated outline; the jejunum did not appear to be abnormal. Gastro-enterostomy afforded relief from the duodenal ulcer, but subsequently tetany and nutritional edema developed. Examination on August 8 revealed an increase in the degree of



Fig. 1 (case 4, Aug. 8, 1930).—Roentgenogram showing smoothing out of the usual contours of the duodenum and jejunum.

smoothing out of the duodenal contour and a smooth outline of the jejunum, with a marked increase in the prominence of the usual outlines of the valvulae conniventes, suggesting edema of the mucosa (fig. 1). The gastro-enteric stoma was functioning well. Examination on June 9, 1931, revealed a marked increase in the degree of the changes observed on the previous examination. The normal markings of the valvulae conniventes were completely absent, and the barium sulphate appeared to "clump up" in smooth masses (fig. 2). There was also some

7. Snell, A. M., and Habein, H. C.: Tetany and Chronic Diarrhea, *Ann. Int. Med.* **1**:694 (March) 1928.

8. Constam, C. R., and Partch, W. T.: An Unusual Case of Nutritional Disturbance, Showing Symptoms of Pellagra, Osteomalacia, and Tetany, *Minnesota Med.* **12**:40 (Jan.) 1929.

9. Snell, A. M.: Chronic Steatorrhea with Tetany: Report of Two Cases, *M. Clin. North America* **15**:1593 (May) 1932.



Fig. 2 (case 4, June 9, 1931).—Roentgenogram showing an increase in the degree and extent of changes in the jejunum since the previous examination. There are dilatation of the jejunum and absence of the usual markings of the valvulae conniventes.



Fig. 3 (case 4, Dec. 1, 1931).—Roentgenogram showing the change in the appearance of the jejunum coincident with clinical improvement. The smoothing out of the jejunal contour is less marked even than in figure 4 and suggests a return toward normal.

dilatation of the small intestine. At this time the colon began to assume a smooth contour, with absence of haustrations. Definite clinical improvement followed this period of observation, and on Dec. 1, 1931, examination revealed regression of the changes observed at the previous visit (fig. 3). The jejunum now compared in appearance with that seen on Aug. 8, 1930. The smoothing out of the contour of the small intestine was less marked, and the outlines of the valvulae conniventes were again discernible. It is significant that the progression of roentgenologic changes was in keeping with the severity of the symptoms, and that definite restoration toward normal marked the clinical improvement of the patient.

CASE 5.—Clinical features of this case have been reported by Curry¹⁰ and Snell.¹¹



Fig. 4 (case 5, Oct. 18, 1932).—Roentgenogram showing the elongated, smoothly outlined masses of barium in the proximal part of the jejunum. There is an absence of the markings of valvulae conniventes in the involved region.

Roentgenologic examination on Aug. 16, 1932, revealed a normal stomach and duodenum. Special study of the small bowel was not made at this time. Therefore, it is possible that alterations in its contour were overlooked. On October 18, the stomach and duodenum appeared to be normal. There was delay in the passage of barium sulphate through the jejunum, and its outline was abnormally smooth (fig. 4). In many places the opaque meal seemed to "clump" in elongated masses similar to those observed in case 4. In many places the barium adhered to the

10. Curry, F. S.: Chronic Steatorrhea with Tetany: Report of a Case. Proc. Staff Meet., Mayo Clin. 7:501 (Aug. 31) 1932.

11. Snell, A. M.: Discussion, Proc. Staff Meet., Mayo Clin. 7:502 (Aug. 31) 1932.

walls of the jejunum after the bulk of the meal had passed, giving it a peculiar, flecked appearance.

CASE 6.—A man, aged 44, complained chiefly of diarrhea, anemia and loss of weight. There was no history of tetany, but roentgenograms of the pelvic bones gave questionable evidence of osteoporosis. The concentration of calcium and phosphorus in the blood was reduced, and there was roentgenographic evidence of disease of the duodenum and jejunum, a matter which will be considered later. This patient was also benefited by the administration of viosterol and calcium lactate and the dietary restriction of fat. Through a period of six months his condition slowly improved, and he gained 6 pounds (2.7 Kg.). Recently an



Fig. 5 (case 6, Oct. 10, 1932).—Roentgenogram of the stomach and jejunum, revealing the smooth contour of the proximal part of the jejunum. Prominent mucosal markings are seen in the duodenum, and there is a tendency of the barium to clump in smooth, elongated masses in the proximal part of the jejunum.

exacerbation of the diarrhea occurred, which may be attributed to dietary indiscretion.

Roentgenologic examination on Feb. 3, 1932, revealed a normal stomach. There was dilatation of the second and third portions of the duodenum, with delay in the third portion suggesting an extrinsic lesion, possibly pancreatic in origin. The motility of the small bowel was observed fluoroscopically, but abnormalities were not noted. A special investigation of the mucosa of the small intestine was not made. An attempt was made to examine the colon by means of an enema of barium sulphate, but the colon was dilated and contained much fluid and barium from previous studies, and an adequate examination was impossible. On October 10, the stomach was reexamined, and a special study of the small bowel was carried out. The stomach was normal, except that its contours were shaggy, suggesting

hypertrophy of the mucosa. The dilatation previously noted in the duodenum was still present, and the contour was somewhat irregular. The jejunum also had a shaggy contour except for areas here and there where the barium clumped in smooth, elongated masses (fig. 5). The caliber of the jejunum appeared to change at different intervals during the examination, and smooth and apparently narrowed regions later were dilated, suggesting the presence of spasm. Motility was delayed.

CASE 7.—A woman, aged 45, had suffered from severe diarrhea, weakness and loss of weight for eight months. Her case is similar to that of the patient in case 6. The difficulty was of short duration, and signs of tetany were absent. The values for blood calcium and phosphorus were reduced, and there was definite secondary anemia. Immediate benefit followed the administration of the same therapeutic procedures as those applied in case 6, but there have since been numerous rather severe relapses, controlled by rigid dietary restriction of fat. At the present time the woman is slowly improving.

Roentgenologic examination of the colon on Feb. 17, 1933, revealed that the lumen was somewhat narrowed and smooth, particularly in the distal portion. There was some smoothing of the outline of the terminal part of the ileum. The stomach and first portion of the duodenum were normal. Barium in the colon prevented study of the small bowel, and the patient did not remain for a second examination.

COMMENT

The general causes of tetany in digestive disorders have recently been reviewed by Marble and Bauer¹² and may be listed as follows: (1) dietary deficiency of either calcium or phosphorus; (2) dietary excess of calcium over phosphorus, or vice versa; (3) deficiency of vitamin D (which may be primary or due to a loss of fat-soluble vitamins in the stools [Linder and Harris]); (4) long-standing diarrhea, especially if large amounts of fat are lost; (5) any condition hindering absorption from the upper part of the gastro-intestinal tract, and (6) biliary or intestinal fistulas of long standing.

The clinical syndrome and metabolic disturbances in chronic steatorrhea with tetany have been ascribed primarily to disturbance in the absorption of fat from the intestine, which in turn prevents proper assimilation of calcium and phosphorus from ingested food. The tetany and decalcification, in other words, represent a calcium-phosphorus deficiency due to faulty absorption. According to Telfer,¹³ the availability of calcium for absorption is dependent on the presence of free hydrochloric acid in the gastric content, which affects the solubility of certain compounds of calcium in the diet. When the alkaline bile and pancreatic juice mix with the content of the upper part of the intestine, calcium is

12. Marble, Alexander, and Bauer, Walter: Calcium and Phosphorus Metabolism in a Case of Nontropical Sprue with Associated Tetany, *Arch. Int. Med.* **48**: 515 (Sept.) 1931.

13. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism: III. The Absorption of Calcium and Phosphorus and Their Fixation in the Skeleton, *Quart. J. Med.* **17**:245 (April) 1924.

precipitated as calcium phosphate. Telfer inferred that absorption of calcium must therefore occur in a relatively small area of the duodenum and upper part of the jejunum. The significance of this observation will be apparent when the known anatomic lesions of idiopathic steatorrhea are considered.

In the condition under consideration, as has been stated, there are deficient digestion and absorption of fat, which may be attributed to some pancreatic disorder, or to some intrinsic lesion of the duodenum or jejunum; the few available observations made at necropsy in these cases tend to substantiate this view. In Whipple's¹⁴ cases there were extensive deposits of neutral fat and fatty acids in the intestinal mucosa and in the mesenteric and retroperitoneal lymph nodes. Chronic passive congestion and cloudy swelling of the viscera were also noted. In Salvesen's¹⁵ case at necropsy were found atrophy of the pancreas and spleen, as well as parenchymatous degeneration of the liver. In the first case reported by Blumgart¹⁶ there were extensive deposits of fat in the intestinal mucosa and in the adjacent lymph nodes; atrophy of the liver and spleen and chylous ascites were also found. In his second case, the changes were somewhat similar. In his third case, discrete ulcers of the ileum and distention of the cecum with atrophy of its mucosa were noted, and deposits of fat in the intestinal mucosa were also observed; these were described as being composed of fat-laden phagocytic cells of unknown origin. In the case reported by Starr and Gardner,¹⁷ atrophy, dilatation and passive congestion of the whole intestinal tract were noted. The mesenteric nodes were hyperplastic, and there were marked atrophic changes in the spleen and pancreas. Hemosiderosis of the liver and spleen were also observed.

On the basis of these anatomic observations, it would appear that in certain cases at least it should be possible to demonstrate roentgenologically evidence of disease in the upper part of the intestinal tract, and such changes have been noted in three of our seven cases. Furthermore, it was apparent in case 4 that the changes became less marked as the patient improved. It is felt that evidence of disease of the upper

14. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, *Bull. Johns Hopkins Hosp.* **18**:382 (Sept.) 1907.

15. Salvesen, H. A.: Observations on Human Tetany: 1. Spontaneous Tetany in Adults, *Acta med. Scandinav.* **73**:511, 1930.

16. Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat: With Emaciation and Anemia, and in Two Acidosis and Tetany, *Arch. Int. Med.* **32**:113 (July) 1923.

17. Starr, Paul, and Gardner, Lois: A Biochemical Study of Two Patients with a Condition Simulating Sprue, *Am. J. Trop. Med.* **10**:283 (July) 1930.

part of the intestinal tract may be of diagnostic value in certain cases of this type.

It is evident from the roentgenologic findings that delayed motility and alterations in the mucosal relief of the small intestine, especially the jejunum, consisting of smoothing of the contours of the lumen, obliteration of the usual markings of the valvulae conniventes and clumping of the barium in elongated masses, occurred in all of our cases in which adequate roentgenologic examination was possible during the active stage of the disease. The roentgenologic findings suggested an inflammatory condition, with edema of the mucosa and infiltration of the walls, involving especially the small intestine and occasionally the stomach, duodenum and colon. The regression of the changes coincident with improvement in the clinical symptoms and inflammatory changes described at necropsy in similar cases would seem to substantiate this opinion. It is not held that these roentgenologic observations are characteristic only of chronic idiopathic steatorrhea, since they may occur in varying degrees in any diffuse inflammatory condition of the intestinal tract. Their presence, however, constitutes tangible evidence, during life, of alterations in the gastro-intestinal tract which have been suspected clinically and found at necropsy in this disease.

The similarity of this condition to sprue has been commented on, but references to roentgenologic studies of the gastro-intestinal tract in that disease are confined to one article by Pillai and Murthi,¹⁸ who investigated nine cases. They found, in the acute forms, no indication of loss of tonus or motility, or other change in the stomach or intestines. In the subacute state there was slight loss of tonus and vigor of peristalsis of the stomach, with consequent delay in passage of content there. The same was true of the cecum and colon. The small intestine emptied rapidly, and spots of barium retained in the upper part of the cecum were interpreted as evidence of ulceration. In the chronic state changes were similar but more marked. There was no evidence of local ulceration of the small bowel. The cecum and transverse colon were dilated, and in one case the transverse colon contained a "pool" of barium. Diverticula observed in the colon were explained by atrophy of the mucosa and fibrotic changes in the muscle which affected the circular fibers before the longitudinal fibers. Pillai and Murthi stated, further, that when there are ulcerations in the mouth and upper part of the alimentary tract, there are no signs of ulceration lower down, and vice versa. From this it is concluded that there are two forms of the disease, the "ascending" and the "descending."

18. Pillai, M. J. S., and Murthi, K. N.: Radiological Signs in Cases of Sprue: A Study of Nine Cases, *Indian J. Med.* **12**:116 (June) 1931; abstr., *Trop. Dis. Bull.* **29**:8 (Jan.) 1932.

Roentgenograms of the skeletal system were made in three of the seven cases with which this paper is primarily concerned.

The bones seemed normal in one case; in the second, there was osteoporosis, and in the third, marked osteomalacia, with deformities of the pelvis and long bones, and pseudofractures (*Umbauzonnen*). The skeletal changes in the last case were so comparable with the roentgenologic changes described by Looeser¹⁹ in cases of hunger-osteomalacia that vitamin deficiency, which may be primary or secondary, is strongly suggested as a cause of the condition.

From the anatomic, physiologic and roentgenologic evidence presented, it is apparent that the clinical syndrome of idiopathic steatorrhea with tetany may be produced by inflammatory or atrophic lesions of the upper intestinal segments. As has been mentioned, the element of defective absorption of fat, mineral salts and vitamins may well be secondary to such lesions. Not all examples of this syndrome present definite intestinal lesions, however, and there is hardly sufficient evidence to justify the belief that the condition constitutes a clinical entity. The same clinical phenomena have been encountered in tropical sprue (Fairley²⁰), which, as recent studies seem to indicate,²¹ may be a deficiency disease approximating in some respects primary anemia. In a recent personal communication, Bauer²² mentioned, among other possible causes of the syndrome, the question of deficient external pancreatic secretion. Holst's²³ recent report of a case of pancreatic carcinoma illustrates this point. Bauer also mentioned the possibility of this syndrome resulting from any disease which would produce a local lesion in the upper part of the intestinal tract, or any disease which would cause sufficient changes in the lymphatic structures of the intestinal tract to interfere with absorption of fat. The mechanical short-circuiting of the small intestine which occurs with gastrocolic or jejunocolic fistula will also produce steatorrhea and defective absorption of calcium, as Fairley and Kilner²⁴ have shown. These possibilities must be considered in any case in which the clinical syndrome under consideration

19. Looeser, E.: Ueber Spatrachitis und Osteomalacie: Klinische, röntgenologische und pathologisch-anatomische Untersuchungen, *Deutsche Ztschr. f. Chir.* **152**:210, 1920.

20. Fairley, N. H.: Sprue: Its Applied Pathology, Biochemistry, and Treatment, *Tr. Roy. Soc. Trop. Med. & Hyg.* **24**:131 (Aug.) 1930.

21. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, *Lancet* **1**:1198 (June 4) 1932.

22. Bauer, Walter: Personal communication to the authors.

23. Holst, J. E.: Ein Fall von pankreatogener Steatorrhöe, *Ztschr. f. klin. Med.* **115**:286, 1930.

24. Fairley, N. H., and Kilner, T. P.: Gastro-Jejuno-Colic Fistula, with Megalocytic Anemia Simulating Sprue, *Lancet* **2**:1335 (Dec. 19) 1931.

is presented, and the etiologic basis for defective absorption of fat and calcium must be sought for in each case.

In the different cases of our series, the previously mentioned etiologic factors varied considerably in significance. In case 4 there was possibly an actual temporary deficiency in diet or in vitamins. The patient often had periods of marked anorexia, and at these times diarrhea and tetany were particularly likely to develop. The principal therapeutic problem in this case was that of providing an adequate intake of food and an ample supply of vitamins. In cases 5 and 6, in which the difficulty was of relatively short duration, the presence of active jejunitis of unknown origin appears to have been of paramount importance. Whether such lesions are primary, or only, as is possibly the case in tropical sprue, a secondary manifestation of deficiency of some unknown substance or substances, cannot be definitely stated. In cases 1 and 2 there was much to suggest a life-long defect in the absorptive power of the upper part of the intestine and in the metabolism of calcium and fat. This statement applies in case 5 in which mild symptoms of tetany had been present for years before diarrhea finally became troublesome. In two of these three cases there was definite evidence of defective growth or of skeletal defects, suggesting persistence into adult life of some inherent abnormality of absorption of fat and calcium.

TREATMENT

Recognition of the fact that there is, fairly commonly, an inflammatory or degenerative lesion of the upper part of the intestine, in idiopathic steatorrhea, should serve, in our opinion, to modify the therapeutic approach. Treatment should meet the requirements laid down by Fairley for the treatment of tropical sprue: (1) rest of the alimentary tract, (2) restoration of the blood to normal and (3) supplying demonstrable deficiencies such as lowered concentration of calcium and of phosphorus in the blood and defective gastric secretion of hydrochloric acid. In our clinical experience with the cases mentioned in this review, it has been apparent that little can be accomplished for these patients unless rest of the alimentary tract and control of the diarrhea have been attained. Dietary regulation becomes, therefore, an essential of successful treatment. In some cases, restriction of the intake of fat and a high intake of protein may control the symptoms. The tolerance to fat appears to be variable. Some of our patients tolerated up to 100 Gm. of fat daily, but others were unable to utilize half this amount. In case 7, the tolerance was low; diarrhea developed if more than 40 or 50 Gm. of fat was given. The tolerance of these patients to fat can best be determined by a stay in the hospital where the excretion and intake of fat can be determined and the two compared. Exact measure-

ments of the amount of fat excreted are not often necessary; the appearance of the stool is characteristic if much fat is being excreted. Carbohydrate tolerance is also variable, as it is in the celiac disease of infants, and has to be determined by trial and error. So-called sprue diets furnish a convenient starting point for dietary adjustment. Proteins are usually tolerated without any particular difficulty, and diets high in protein have been used with particular success in treatment of the acute phases of the disorder. As the condition of the patient improves, fats and carbohydrates may be added.

The use of vitamin D, in the form of viosterol, appears to be of great therapeutic value. This fact is borne out by the experience of numerous workers. Bauer and Marble, after the administration of viosterol, noted prompt increase in absorption of calcium and phosphorus, elevation of the values for serum calcium and serum phosphorus, establishment of a positive calcium and phosphorus balance and marked improvement in clinical symptoms. Their observations may be taken as further evidence of the relationship of the syndrome just described to infantile tetany and rickets. Viosterol alone may suffice to keep the diarrhea and the depletion of calcium under control, but as a rule dietary regulation is also necessary.

Parathyroid extract-Collip is obviously only a symptomatic remedy in these cases, since it does not increase the utilization of calcium but causes increased liberation of this substance from the skeleton. In the presence of severe fatty diarrhea, its characteristic effect on the value for blood calcium is often obtained only with large doses. It appears to have little effect on the symptoms of diarrhea in many cases, although in Holmes and Starr's²⁵ cases it exerted a generally beneficial effect. As a means of controlling tetany it is highly effective, but its use should be continued only when necessary, the patient's bodily store of calcium meanwhile being fortified by large doses of calcium lactate given by mouth.

The anemia associated with this condition may often be a problem in itself. In a number of cases it has been of sufficient severity to simulate primary anemia, and in fact is distinguished from the latter condition chiefly by the presence of free hydrochloric acid in the gastric content and the absence of changes in the spinal cord. In the treatment of this sprue type of anemia, liver extract has been used with good effect, and Porter and Rucker²⁶ have described two cases in which the diarrhea was also greatly relieved by its use. Our own experience with

25. Holmes, W. H., and Starr, Paul: A Nutritional Disturbance in Adults Resembling Coeliac Disease and Sprue, *J. A. M. A.* **92**:975 (March 23) 1929.

26. Porter, W. B., and Rucker, J. E.: The Treatment of Nontropical Sprue with Liver Extract, *Am. J. M. Sc.* **179**:310 (March) 1930.

liver therapy has been limited, one patient (case 5) having apparently been originally made worse by its use; later he used liver extract with excellent effect. Marmite, a substance derived from yeast, has also been described by Vaughan and Hunter ²⁷ as having a specific effect on the anemia of this disease.

CONCLUSION

In general, it may be said that if the diarrhea is kept under control, neither the depletion of calcium nor the changes in the blood will reach serious proportions. The treatment in these cases is, as we have already emphasized, a highly individualized problem, and one which calls for considerable resource on the part of the physician. It is well to remind the patient in advance that immediate good results do not necessarily mean freedom from relapses in the future. The best therapeutic responses have been obtained with cooperative patients who were willing to submit readily to changes in diet and medication, and to tolerate a certain amount of discomfort from these sources.

The prognosis appears to be fairly good. If the bones show extensive demineralization, the outlook is obviously not so favorable, although it is not necessarily hopeless. In cases in which the factors of dietary or vitamin deficiency predominate, much can be expected from treatment. In cases in which there are extensive pancreatic or intestinal lesions, there is reason to believe that greater difficulties will be encountered. The case reported by Radl and Fallon is in point. The whole matter of treatment may be summarized by the statement that it is wise to evaluate the most important etiologic factors in the individual case and then to direct treatment accordingly. Early diagnosis is imperative and should cause no difficulty, if the condition is considered when diarrhea is an outstanding factor. An excess of fat in the stools and reduction in values for blood calcium and blood phosphorus should assist in establishing the diagnosis. The roentgenologic appearance of the small bowel, although probably not specific for this disorder, may be of confirmatory value.

27. Vaughan, Janet M., and Hunter, Donald: The Treatment by Marmite of Megalocytic Hyperchromic Anaemia, *Lancet* 1:829 (April 16) 1932.

News and Comment

COMING MEETINGS

American Medical Association, Cleveland, June 11-15, 1934.

American Society for Clinical Investigation, Hotel Chalfonte-Haddon Hall, Atlantic City, N. J., April 30.

Association of American Physicians, Atlantic City, N. J., May 1 and 2.

Book Reviews

Metabolic Diseases and Their Treatment. By Erich Grafe. Translated by Margaret Galt Boise, under the supervision of Eugene F. DuBois, M.D., and Henry B. Richardson, M.D. Price, \$6.50. Pp. 551. Philadelphia: Lea & Febiger, 1933.

Nothing except in praise can be said of this excellent translation of Professor Grafe's treatise. The author is well known in this country as a student of metabolic problems, and a systematic exposition of his views will be welcome to all physicians. The book is one of those rare ones in which a really profound and scholarly discussion of the fundamentals of a subject by one conversant with them at first hand is combined with sound clinical knowledge. There are general sections on metabolism and on the chemistry of foods, followed by a discussion of the nature and treatment of nutritional disorders. Special sections follow on obesity, undernutrition and diabetes, to the last of which some 200 pages are devoted. Gout and other "inborn" errors of metabolism are dealt with next, and finally come sections on diabetes insipidus, calcareous diathesis and the formation of stones. The general plan with each subject is to analyze the underlying pathologic physiology and on this superstructure to erect the clinical discussion. The entire material is thoroughly documented with a full representation of American as well as foreign literature. Specialists will, of course, always disagree on minor points, but in this book all sides of the question are fairly presented, even though the author emphasizes his own views. The only point which I am inclined to criticize is the consideration given to a large number of German proprietary pharmaceuticals which, aside from their euphonious names, probably have little virtue.

Congrès français de médecine, Twelfth Session, 1932. Report 1: The Anatomic and Clinical Character of Malignant Granuloma.

This is an exhaustive study and review of all possible types of Hodgkin's disease, in an effort to place it definitely as a borderline inflammatory state, different from a purely neoplastic state, of the reticulo-endothelium. Confusion arises in the histologic picture, because the lesions show in a haphazard way all the polymorphic evolutionary and progressive changes that the mesenchymal tissue is capable of undergoing (inflammatory, fibrous and neoplastic) and follow stimulation by the virus. Even the cells of Sternberg are thought to be otherwise normal megakaryocytes. Stress is laid on the presence of eosinophils, the possible absence of the cells of Sternberg and, particularly, the presence of pruritus.

High voltage penetrating roentgen therapy produces the only remission of any duration. Suspected areas should be treated, but no prophylactic doses should be given. Superficial lesions should receive from 750 to 1,200 roentgen units, divided into daily doses, for from ten to fifteen days. Deep-seated lesions should receive from 4,000 to 5,000 roentgen units, from 1,000 to 1,200 units through each field. The treatment should last for from four to five weeks. The tension is set at from 180 to 200 kilovolts and the intensity at from 2 to 4 milliamperes, with filtration through from 0.5 to 1 mm. of copper and 1 mm. of aluminum.

Biologic and bacteriologic experiments have not proved any factor to be etiologic. Tuberculosis seems to have more than a casual relation, but no definite connection can be established.

The Modern Treatment of Syphilis. By Joseph Earle Moore. Price, \$5. Pp. 535. Springfield, Ill.: Charles C. Thomas, Publisher.

From time to time books appear which stand out as landmarks in a subject so far as they rid themselves of the deadwood of tradition and by a consideration of actual facts formulate definitely a new point of view. Such a result, in our opinion, has been achieved by Moore in his discussion of the modern treatment of syphilis. Above all, he has stated clearly and on a rational basis the imperative reasons for prolonged, intensive and continuous treatment in early syphilis; in contrast with the widely different indications for therapy in the late stages, when the patient has built up his own immunity. Each phase of the subject is gone into in detail, and the conclusions are based on actual statistical material from the author's clinic or from the literature, and not on vague general impressions. One of the most attractive features of the book is that it is a personal one. Dr. Moore tells the story as he sees it, in a terse, dramatic style. Once started, it is hard to put the volume down as the thread of the argument unrolls. Here and there one may differ on fine points; this to the reviewer is a healthy sign; the author who completely protects himself against challenge produces at best a dreary compendium.

Space forbids a detailed discussion of the extensive material which Dr. Moore has handled; suffice it to say that there are chapters dealing with the biology of syphilis, with the various antisyphilitic drugs and special procedures, with the details of treatment of all forms and phases of syphilis, with the serologic problems and finally with the social aspects of the disease. The illustrations and charts supplement admirably the discussion in the text, and each chapter is followed by a well selected bibliography.

Arritmias. By Antonio Battro. Pp. 246, with 141 illustrations. Buenos Aires: Sebastian de Amorrortu, 1933.

This paper-bound volume presents an excellent discussion of the cardiac arrhythmias. It devotes several pages to the anatomy of the heart and then proceeds with a description of the methods of registering graphically the cardiac irregularities. One criticism might be interpolated: Much more space is devoted to the study of the cardiac rhythm by means of polygraphs and polygraphic tracings than in this country. That seems like a waste of time. The latter half of the book deals with the various types of arrhythmias from the point of view of the accompanying physiologic disorders, the clinical expression of the mechanistic disturbances and their polygraphic and electrocardiographic expressions.

The make-up and format of the book are excellent; the paper is of a high grade glossy quality on which the numerous figures are excellently reproduced. The book may be highly recommended to physicians who can read Spanish.

Principles of Human Physiology. By E. H. Starling. Edited and Revised by C. Lovatt Evans. Sixth edition. Pp. 1,122. Philadelphia: Lea & Febiger, 1933.

Professor Evans' recent revision of Starling's Physiology maintains, we believe, in every respect the high standards of the University College group. The tendency naturally is to stress the principles of general physiology, but the wider philosophy of the subject is so admirably blended with the special aspects of human physiology that whether the reader be biologist or medical student his needs are adequately served. Recent points of view receive thorough discussion, and the entire book bears evidence of critique and authoritative analysis. The format is attractive; the illustrations are good, and the references—mostly dealing with comprehensive articles—are carefully selected.

ETIOLOGY AND SYMPTOMS OF NEURO- CIRCULATORY ASTHENIA

ANALYSIS OF ONE HUNDRED CASES, WITH COMMENTS
ON PROGNOSIS AND TREATMENT

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AND

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The term "neurocirculatory asthenia," adopted in America during the World War, and synonymous with the less satisfactory British expression "effort syndrome," was applied in an attempt to classify a large number of persons having symptoms referable to the cardiovascular system not dependent on any known pathologic process of the heart or blood vessels but often associated with a functional nervous disturbance. These symptoms were chiefly palpitation, shortness of breath, precordial pain or discomfort and exhaustion. One or more associated symptoms were often present: faintness, syncope, headache, dizziness, insomnia, increased perspiration, difficulty in swallowing, tremor, flushing and pallor. The borderline between the normal and the abnormal is ill defined, but neurocirculatory asthenia may be said to be present when the symptoms appear during such customary physical activities and excitements of daily life as previously caused no symptoms or which in the average person produce no symptoms.

Neurocirculatory asthenia is of great importance because of its frequency, because of the marked suffering and even invalidism that it may cause and especially because of the need for its proper recognition and early treatment. There has been much confusion concerning this syndrome; it is to be distinguished from irritability of the heart alone shown by premature beats or paroxysmal tachycardia. It is also to be distinguished from psychoneurosis as such, in which anxiety, hypochondriasis or hysteria is predominant. However, many of the persons of the neurocirculatory asthenic group are definitely neurotic or psychoneurotic, as noted by Rothschild¹ and others. Neurocirculatory asthenia is a much better term than effort syndrome, since the latter may be produced in normal people. The symptoms comprising effort syndrome in normal people are not exactly the same, as a rule, as the symptoms found in neurocirculatory asthenia; for example, precordial

1. Rothschild, M. A.: Neurocirculatory Asthenia, Bull. New York Acad. Med. 6:223, 1930.

aching is more commonly found in the latter syndrome, while breathlessness is almost the universal complaint in the effort syndrome of normal people. The early designation "disordered action of the heart" of the British included cases of organic heart disease; furthermore, in the purely functional cases, such a term focused the patient's attention on his heart, a practice which is to be discouraged.

To throw more light on the subject of neurocirculatory asthenia we have analyzed the etiologic relationships and symptoms of patients seen by us in civilian life, particularly of 100 persons in hospitals and private practice encountered during the past few years: 50 patients without heart disease and 50 patients with heart disease.

LITERATURE

Hippocrates recognized that palpitation might result from emotion or excitement. Galen devoted part of his sixteen books on the pulse to the influence of the various emotions on the heart. Corvisart² in 1806 recognized that palpitation might be a symptom of no danger. In 1870 Austin Flint³ wrote that "persons who make complaint of symptoms referable to the heart may suffer from a functional disorder only." Neurocirculatory asthenia includes most of the cases described in 1871 by Da Costa⁴ as "irritable heart" and those of "disordered action of the heart" and "effort syndrome" of the British⁵ during the World War (1914-1918). Other names, such as "vasomotor neurosis" and "soldier's heart" have also been used as designations of this condition.

As noted by Rothschild,¹ Brooks⁶ and others, the medical profession did not appreciate the importance and frequency of this syndrome before the war of 1914-1918, in spite of the rather extensive literature on the subject, and even today (1933) it is but little recognized by many physicians. Most articles have dealt with the presence of this condition in soldiers, but it is also a common occurrence in civilian life.

2. Corvisart, J. N.: *Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux*, ed. 1, Paris, Migneret, 1806.

3. Flint, A.: *Functional Disorder of the Heart, A Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart*, Philadelphia, Blanchard & Lea, 1859, p. 403.

4. Da Costa, J. M.: *On Irritable Heart*, *Am. J. M. Sc.* **61**:2, 1871.

5. Lewis, T.: *The Soldier's Heart and the Effort Syndrome*, New York, Paul B. Hoeber, Inc., 1919.

6. Brooks, H.: *Syncope in Neurocirculatory Asthenia*, *Tr. A. Am. Physicians* **39**:419, 1924; *Neurocirculatory Asthenia*, *M. Clin. North America* **2**:477, 1918; *Functional Disturbances of the Heart*, Philadelphia, J. B. Lippincott Company, 1932.

Of a series of 3,000 patients with cardiac symptoms or signs who sought medical advice, both in hospitals and in private practice in recent years in New England (White and Jones, 1928⁷), 302, or 10 per cent, were found to have neurocirculatory asthenia alone and 62, or 2 per cent, were found to have neurocirculatory asthenia complicating organic heart disease; nearly 3 per cent of the 2,315 cases of organic heart disease showed well marked neurocirculatory asthenia.

PRESENT STUDY

In the series of 100 cases presented here group I consists of 50 cases of pure neurocirculatory asthenia, having no heart disease demon-

TABLE 1.—*Symptoms in Neurocirculatory Asthenia*

	Group I (50 Cases) Without Organic Heart Disease		Group II (50 Cases) With Organic Heart Disease		Total per Cent of 100 Cases
	Number Cases Having	Per Cent of Group	Number Cases Having	Per Cent of Group	
Palpitation.....	40	80	38	76	78
Respiratory discomfort.....	39	78	38	76	77
Precordial pains or aches.....	32	64	42	84	74
(with radiation of pain).....	16	32	17	34	33
Exhaustion or easy fatigability.....	34	68	39	78	73
Functional gastro-intestinal symptoms...	20	40	24	48	44
Faintness.....	18	36	20	40	38
Syncope.....	10	20	9	18	19
Headache.....	15	30	22	44	37
Dizziness.....	16	32	21	42	37
Insomnia.....	9	18	21	42	30
Increased perspiration.....	10	20	8	16	18
Tremor.....	9	18	4	8	13
Flushing.....	5	10	5	10	10
Pallor.....	7	14	1	2	8
Precordial tenderness.....	11	22	6	12	17
Globus hystericus.....	4	8	7	14	11

strable by physical, electrocardiographic and roentgen examination, while group II consists of 50 patients with organic heart disease complicated by neurocirculatory asthenia. Twenty-five patients with "neurasthenia," group III, and a like number with psychoneurosis, group IV, have also been studied with particular reference to the frequency of occurrence of the cardinal symptoms of neurocirculatory asthenia when this syndrome as such did not exist in the latter groups. The borderline between neurasthenia and neurocirculatory asthenia is very vague, and certain of the cardinal symptoms of neurocirculatory asthenia may occur in the patients of the former group when the chief complaint is not referable to the cardiovascular system. In groups III and IV all

7. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, Am. Heart J. 3:302, 1928. White, P. D.: Cardiac Neuroses, in Nelson Loose Leaf Medicine, New York, T. Nelson & Sons, 1920, vol. 4, p. 635; 1931 edition, vol. 4, p. 447; An Important Consideration in the Analysis and Management of Heart Trouble: 4 Cases, New England J. Med. 199:148, 1928.

patients were excluded whose chief complaints were related to the cardiovascular system or whose conditions were diagnosed as neurocirculatory asthenia, effort syndrome or cardiac neurosis.

ETIOLOGIC DATA

Age.—The average age in these civilian cases was higher than that among soldiers during the war, doubtless because we are dealing with all ages in the community. The fact that young people in civilian life are ordinarily not subject to as much strain as soldiers during war is probably another factor of significance. The ages at the onset of symptoms in our group of 100 cases ranged from 12 to 69 years, with the average age $35\frac{3}{4}$ years ($31\frac{1}{2}$ years in pure neurocirculatory asthenia and 40 years for the group with complicating organic heart disease). There were 9 patients in the second decade, 25 in the third, 34 in the fourth, 21 in the fifth, 6 in the sixth and 5 in the seventh.

TABLE 2.—*Symptoms in Neurocirculatory Asthenia*

	Group III (Neurasthenia, 25 Cases)		Group IV (Psychoneurosis, 25 Cases)		Total per Cent of 50 Cases
	Number Cases Having	Per Cent of Group	Number Cases Having	Per Cent of Group	
Palpitation.....	12	48	9	36	42
Respiratory discomfort.....	9	36	8	32	34
Precordial pains or aches.....	8	32	7	28	30
Exhaustion.....	10	40	4	16	28

It is of interest that Lincoln⁸ reported five instances of what she described as effort syndrome in children from 4 to 9 years of age, the group consisting of 3 boys and 2 girls; such early incidence is rare.

Sex.—The females outnumbered the males. 69 to 31, the percentage of females being slightly higher in group I than in group II (37 to 32). Twenty-two of the patients were unmarried (15 per cent of group I, 7 per cent of group II). Sexual irregularities or unhappy marriages played an important rôle in initiating symptoms in 4 patients of group I and in 1 patient of group II.

Constitutional Type.—As to the type of build most often affected, only 9 per cent of the patients were poorly developed or undernourished, while the majority, 81 per cent, were well developed and well nourished or obese (18 per cent); the remaining 10 per cent fell between these extremes. It is the common belief that the person of asthenic build is the most common type; we did not find this to be true.

Ninety-eight of our 100 patients were white and 2 were Negroes.

8. Lincoln, E. M.: The Hearts of Normal Children, *Am. J. Dis. Child.* **35**: 398 (March) 1928.

Occupation.—People engaged in almost all occupations were represented among our patients, housewives, trained nurses, teachers, clerks, students and doctors comprising the greater percentage, with the housewives predominating (51 per cent). Ninety-one per cent had sedentary occupations while only 9 per cent performed laborious tasks.

Causative Factors.—The factors initiating symptoms or contributing to them are numerous; in fact, in many cases it is difficult properly to evaluate these factors, especially when several factors seem to be playing a part. In the group in which there is a definite neurogenic element present (classification, p. 639), we encounter many people in whom symptoms of neurocirculatory asthenia develop on slight provocation, while in others the symptoms develop only after many trying experiences. The neurogenic element may vary from a mere state of anxiety to psychoneurosis, epilepsy or insanity. Four per cent of our patients had epileptiform seizures, while one patient was definitely paranoid. Oppenheimer and Rothschild⁹ found a family history of epilepsy in 15 per cent and of insanity in 23 per cent of 100 cases of neurocirculatory asthenia studied by them, while in the same number of controls there was a negative history for both epilepsy and insanity. Boas¹⁰ stated that "the anxiety neurosis, and the varied psychic disturbances that contribute so largely to the development of the picture of neurocirculatory asthenia may be regarded as producing excessive and exaggerated stimuli which reflexly affect the heart through the corticomedullary pathways, whose course is still unknown."

Such a factor as anxiety over family, finances or disease is often contributory. Sexual irregularities, such as maladjustment, overindulgence or an unhappy marriage, may be an evidence of the neurogenic element. In several of our patients with changes due to pregnancy or to the menopause, the physiologic processes were found to upset the delicate balance of persons previously considered normal and to initiate symptoms of neurocirculatory asthenia. It is apparent that these persons did not have the normal reserve, that something was lacking in their make-up. This lack of normal reserve varied greatly in different patients. The others (10 per cent) showed symptoms only on marked provocation, as persons who had worked hard for many years without a vacation or who had worked without sufficient daily rest.

Infectious diseases or operations are sometimes responsible for initiating symptoms of neurocirculatory asthenia; 9 per cent of our patients belonged to this group. Scarlet fever, pneumonia, infections

9. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, *J. A. M. A.* **70**:1919 (June 22) 1918.

10. Boas, E. P.: Neurogenic Disorders of the Heart, *Am. J. M. Sc.* **176**:789, 1928.

of the upper respiratory tract and arthritis were the infections noted in our patients. Grant,¹¹ Lewis⁵ and others have observed that malaria, rheumatic fever and gastro-enteritis, as well as many other infectious or constitutional diseases, may be the initiating factors. We found that often there is an interplay of the infectious and neurogenic elements, as suggested by Gunewardene.¹² In support of this view, we have noted a few patients in whom symptoms have persisted for years after recovery from some infectious disease. The postinfectious group usually complains of exhaustion primarily and to a less extent of dizziness and palpitation; however, in those of dual origin precordial pain and shortness of breath may become prominent after a time.

We made observations concerning the use of coffee, tea, alcohol and tobacco in our group. It was found that 33 per cent of the 100 patients used no coffee or tea, and 79 per cent no tobacco, while 89 per cent abstained from alcohol; 56 per cent used moderation in respect to coffee, 37 per cent to tea, 11 per cent to tobacco, and 9 per cent to alcohol; this leaves only a small percentage that indulged excessively. Seldom did a patient use more than two of the aforementioned substances. It was not unusual for a patient to volunteer that he or she was sensitive to one or more of them, and a few patients had symptoms only after alcoholic sprees or excessive use of tobacco or coffee. This is in contrast to the habits of 100 controls of exactly the same sex and age distribution and of the same social status (50 of them with organic heart disease): 23 per cent used no coffee or tea, 62 per cent no tobacco and 69 per cent no alcohol. We conclude, therefore, that coffee, tea, alcohol and tobacco are not causes of neurocirculatory asthenia, although they may be aggravating factors, and that persons with or subject to neurocirculatory asthenia indulge in these things less than do other members of the community without neurocirculatory asthenia.

Nearly one half (44 per cent) of our patients suffered from some functional gastro-intestinal complaint, varying from occasional nausea, vomiting, or heart-burn to frequent episodes of severe abdominal distress, which in no case proved after careful study to be of organic origin. It has been noted before that many patients whose chief complaint is referable to the gastro-intestinal tract also complain of one or more of the cardinal symptoms of neurocirculatory asthenia.

Disease of the thyroid gland had occurred as a past event in 2 of the 100 patients, thyrotoxicosis in 1, in group I, and colloid adenoma in the other, in group II. The patient of group I was a woman

11. Grant, R. T.: Observations on the After Histories of Men Suffering from the Effort Syndrome, *Heart* **12**:121, 1925.

12. Gunewardene, H. O.: The Etiology of Effort Syndrome, *Lancet* **1**:885, 1920.

42 years old, who had had symptoms for a year, including: fleeting pains in the precordium radiating to the left arm, palpitation, shortness of breath (sighing), flushing, exhaustion, loss of weight and a slight increase of perspiration. She was operated on for the hyperthyroidism with a control of that factor; examination of the excised gland revealed primary hyperplasia; the basal metabolic rate, which had been plus 22 per cent before surgical intervention, dropped to minus 12 per cent after operation. However, when seen by us fifteen months after the operation she complained of attacks of fast pulse (probably paroxysmal tachycardia) and fleeting precordial pain radiating to the left axilla. She sighed frequently and was found to have no evidence of heart disease. The second patient was a woman 52 years old with hypertensive heart disease, chronic arthritis, colloid goiter and perhaps a slight hyperthyroidism (basal metabolic rate plus 20); she had had symptoms referable to the heart for two years. Two years after thyroidectomy the symptoms had abated very little. In both cases the neurocirculatory asthenia continued with little or no improvement after the disease of the thyroid gland had been eradicated. Of course, effort syndrome simulating neurocirculatory asthenia is the rule when thyrotoxicosis is present.

While neurotic and psychoneurotic patients may have neurocirculatory asthenia, it is also true that many of them have no symptoms referable to the cardiovascular system. In reviewing cases of neurasthenia and psychoneurosis, it was noted that in a number of them one or more of the cardinal symptoms of neurocirculatory asthenia was present, though these were not chief complaints and were elicited only on close inquiry.

It is our belief that usually in the histories of the patients with neurocirculatory asthenia possible neurotic or psychoneurotic factors are not sufficiently investigated. Rothschild and Oppenheimer⁹ thought that psychoneurosis and the "irritable heart" of soldiers might result from a common but as yet unknown cause. They have suggested that such factors as enuresis, childhood frights, excessive absorption in religion and moodiness should be considered in the analysis and classification of neurocirculatory asthenia. We believe that definite neurogenic elements can be discovered in at least 75 or 80 per cent of these patients.

Based on the etiologic data studied, we suggest the following useful etiologic classification of neurocirculatory asthenia:

Type A:

- (1) That which follows severe infection, operation, or other illness.
- (2) That following prolonged, fatiguing work or strain of some other sort without respite.

Type B:

- (1) That following a slight to moderate infection, operation or other illness.
- (2) That following a moderate amount of fatiguing work or a strain of any sort.

Type C:

That occurring after little or no strain, but much aggravated by illness or fatigue.

A (1) and (2) may occur in people with normal constitutions, B (1) and (2) in the borderline group and C in those who are definitely inferior constitutionally. There may be combinations of A (1) and (2), A (1) and B (2), B (1) and (2), or B (1) and A (2).

According to this classification, 9 per cent of our patients belonged to group A (1) and 10 per cent to A (2), while 61 per cent belonged to group B and 20 per cent to group C.

SYMPTOMS AND SIGNS

We found that four symptoms, namely, palpitation, respiratory discomfort, precordial distress and exhaustion, occurred with almost the same frequency (from 73 to 78 per cent) in our 100 patients; they may be called the cardinal symptoms of neurocirculatory asthenia. Other symptoms which are often or sometimes noted are: faintness, syncope, insomnia, headache, dizziness, increased perspiration, difficulty in swallowing, tremor, flushing and pallor. These symptoms occur with almost the same frequency in patients with pure neurocirculatory asthenia as in those having an associated organic heart disease (table 1).

Palpitation was slightly more common in group I (80 per cent) than in group II (76 per cent) and usually consisted of the subjective sensation of pounding or of forceful beating of the heart at either a normal or a rapid rate. Occasionally a patient with pure neurocirculatory asthenia complained of irregular palpitation, but for the most part it was described as fast and regular. As expected, patients of group II complained more often of an irregular palpitation, since all of these patients had organic heart disease. Often palpitation only occurred after an emotional upset or after exercise. The pulse rate is often 150 or 160 or more after some slight stimulus and gradually returns to normal, usually requiring a much longer time to do this than in normal persons. Several of our patients with a pulse rate of from 80 to 90 during rest, experienced an acceleration to 140 to 160 simply through the excitement of having an electrocardiographic tracing made. A few patients were aware of palpitation only at night when in bed, especially when lying on the left side. Others were conscious of the heart beating most of the time, though it might be at a normal rate. Premature beats were infrequent in the cases of pure neurocirculatory

asthenia (once in 50 cases), but they may occur with regularity, even producing a bigeminal rhythm of the pulse. When bigeminy is present it usually disappears after exercise. It should be emphasized that the term "irritability of the heart" as used at the present time often refers to a normal heart having either auricular or ventricular premature beats. Frequently such patients are conscious of extrasystoles, but seldom do they suffer from neurocirculatory asthenia.

Respiratory discomfort or even actual dyspnea was the second most common symptom (77 per cent), and like palpitation it was more often subjective than objective, being an unpleasant consciousness of the ordinary respiratory act without much evident labor, distress or rapidity of respiration. Sometimes, however, there is tachypnea, and during the World War patients were noted with extreme but temporary acceleration of the respiratory rate, even to 100 or more per minute. The dyspnea may occur during rest, but more often it comes on after excitement or from slight to moderate exertion, depending to some extent on the degree of neurocirculatory asthenia. If the dyspnea occurs at rest, the patient when questioned usually answers that he or she feels as though not enough air were getting into the lungs and that therefore it is necessary to take a long breath, which is often evidenced by a deep, sighing inspiration. This is a useful sign in confirming the diagnosis of neurocirculatory asthenia. Sighing was recorded in 35 per cent of the cases of the present series; it was noted in 80 per cent of 100 cases reported by White and Hahn.¹³ During rest in neurocirculatory asthenia the respiratory rate is usually normal or only slightly increased in rate, while after exercise it is often increased out of proportion to the amount of exertion and may be much shallower than normal. Often a patient will complain that he or she has had to give up some sport because of shortness of breath or exhaustion.

Precordial pain or discomfort occurred in 74 per cent of our patients, somewhat more commonly in those with organic heart disease (84 per cent in contrast to the 64 per cent of the patients without organic heart disease). It varies from an occasional "heartache," usually a constant dull aching or burning sensation, to the sharp needle-like or knifelike pain which lasts a few seconds, but which may recur over periods of minutes to hours. The location, character and duration of the pain or discomfort of neurocirculatory asthenia clearly distinguish it from angina pectoris. Radiation of the precordial discomfort of neurocirculatory asthenia to the left arm, axilla, shoulder,

13. White, P. D., and Hahn, R. G.: The Symptom of Sighing in Cardiovascular Diagnosis: With Spirographic Observations, *Am. J. M. Sc.* **177**:179, 1929.

scapula or even to the right arm may occur (as in 33 of 74 patients of our series; once to the neck and once to both arms). The more severe the discomfort, the more likely the radiation. Usually the discomfort occurs over the apex or lateral wall of the chest, but it may involve the whole left side of the chest. Not infrequently women complain of soreness or pain in or just under the left breast, which is not dependent on disease of the breast, but is evidence of the discomfort just described. Precordial tenderness not infrequently occurs in these patients and may also be present even when there is no precordial discomfort (1 of 17 cases); when present either with or without precordial discomfort, it is an important confirmatory sign of neurocirculatory asthenia.^{14a} The examiner should not inquire regarding precordial tenderness until he has closely observed the patient's facial expression during the palpation of the chest.

Exhaustion or easy fatigability occurred in 73 per cent of the 100 cases, occurring in varying degrees. It may be constant or intermittent, occurring only at the time of, or sometimes apparently initiating, an episode of neurocirculatory asthenia. Exertion or emotional strain seems to increase the ease of fatigability.

An attempt was made to determine the most frequent combination of symptoms. It was found that precordial distress, palpitation and shortness of breath occurred in 49 per cent of our patients, pain and palpitation without shortness of breath in another 11 per cent, pain and shortness of breath without palpitation in 10 per cent and pain alone in 4 per cent. Fifty-three of 74 patients (72 per cent) with pain also complained of exhaustion. In the group without pain other combinations of symptoms occurred: palpitation, shortness of breath and exhaustion (15 per cent), palpitation and exhaustion (2 per cent), shortness of breath and exhaustion (3 per cent) and palpitation and shortness of breath (2 per cent). In the remainder, various other combinations of the associated symptoms occurred.

Lewis⁵ stated that syncope occurs not infrequently with "the effort syndrome" (neurocirculatory asthenia), while others believe that it occurs only rarely. It was noted in 19 per cent of our patients, but in them not often as a rule; in a few cases it happened frequently, even up to several times a week. Faintness is a much more frequent symptom than syncope; we found it in 38 of our group of 100 patients. It may occur after emotional strain or may be present only when the patient experiences some of the cardinal symptoms of neurocirculatory asthenia. It may or may not precede syncope. It is often accompanied

14a. Kellogg, F., and White, P. D.: The Clinical Significance of Precordial Tenderness—The Relationship of Such Tenderness to Pain, *New England J. Med.* 206:659, 1932.

by dizziness. Culpin^{14b} stated the belief that these attacks of faintness originated with anxiety and are primarily of emotional origin, being identical with the "nervous attacks" of the sufferer with an anxiety condition. He further stated that "there is no line to be drawn between these attacks and others, usually called hysterical, in which emotion finds expression in motor activity."

The symptom of increased perspiration occurred in 18 per cent of our cases, tremor in 13 per cent, flushing in 10 per cent and pallor in 8 per cent; these may be considered as confirmatory symptoms of neurocirculatory asthenia, but when existing alone they certainly are not diagnostic of it. Increased perspiration may be a troublesome complaint. Insomnia is rather frequent in neurocirculatory asthenia, having occurred in 30 per cent of our cases. Eleven patients complained of symptoms suggestive of globus hystericus, varying from a choking sensation when tired to a full sized globus.

Emphasis should be placed on the frequency with which functional gastro-intestinal symptoms accompany neurocirculatory asthenia; this happened in 44 per cent of our series. These gastro-intestinal symptoms vary from an occasional spell of nausea, vomiting or slight, shifting abdominal distress to frequent and severe symptoms.

In attempting to determine the most frequent "chief complaint" at the time of the patient's first visit to us, it was found that often there were several symptoms almost equally prominent in the same patient. The cardinal symptoms of neurocirculatory asthenia which occurred as chief complaints are: precordial pain or distress in 41 per cent of our patients (in addition, angina pectoris occurred six times in group II), shortness of breath in 35 per cent, palpitation in 34 per cent and exhaustion in 25 per cent.

In group II (patients with neurocirculatory asthenia and organic heart disease) the symptoms were essentially the same in character and quantity as in group I, the cardinal symptoms occurring with approximately the same frequency in each group, as noted in table 1. The greater frequency of precordial pain, aching or distress in group II can possibly be explained by a greater consciousness of the heart, due to the fact that 26 of 50 patients of this group had enlargement of the heart. In group II there were 14 cases of hypertensive heart disease, 14 cases of coronary disease, 1 case of syphilitic aortitis and 29 cases of rheumatic heart disease, with 15 of the last named group showing lesions of both the aortic and the mitral valve. Several of the 50 patients in group II showed combined etiologic factors; 3 of the patients with hypertension had evident coronary disease, 3 of those with

14b. Culpin, M.: The Psychological Aspects of the Effort Syndrome, *Lancet* 2:184 (July 24) 1920.

rheumatic heart disease had coronary disease, and the 1 with syphilitic aortitis had coronary disease; hypertension occurred in 2 of the group with rheumatic heart disease. Seven patients suffered from angina pectoris, while 4 had either definite or suggestive histories of coronary thrombosis. Of the 29 patients with rheumatic heart disease, 17 gave definite histories of acute rheumatic fever and 1 other of chorea, while 11 gave no history of chorea or rheumatic fever; of these 11 patients, 2 had had scarlet fever, 3 frequent tonsillitis and 2 others pains in the joints or muscles without definite rheumatic fever. In 1 patient the neurocirculatory asthenia began several years before the attack of rheumatic fever, while in the others the rheumatic infection antedated the neurocirculatory asthenia by at least two years. Only 2 patients of group I had rheumatic fever.

It is important to realize that although a person may have definite organic heart disease, his or her symptoms may be, and often are, entirely on a functional basis not originating in the heart lesion. This happened in the case of a considerable proportion of the patients in group II, at least 70 per cent, while the symptoms of the remaining 30 per cent were also chiefly functional.

SIGNS

Size of the Heart.—A roentgenogram taken at a distance of 7 feet, a fluoroscopic examination or an orthodiagram was obtained of 41 of the 50 patients in group I, and in no instance was the heart enlarged, whereas a definite tendency toward a decreased cardiothoracic ratio was noticed in the poorly nourished patients as well as in several of those described as being well developed and nourished. Of the patients in group II, 14 had hearts of normal size, while 36 had from slight to moderate enlargement as shown by physical and roentgen examinations.

Murmurs.—Fifty per cent of group I had "functional" systolic murmurs, for the most part apical but often pulmonary, which were described as soft or faint. The murmurs were not increased after exercise and were usually lessened by deep inspiration.

Blood Pressure.—In group I the systolic blood pressure in 4 of 49 instances was above 150 mm. of mercury on the first examination, while subsequent readings for the same patients showed the pressure to be much lower. The same variation was found to be true for the diastolic pressures. In our group the blood pressures closely approximated those of normal persons of the same age and weight. The average pressure for group I was 129 mm. of mercury systolic and 78 mm. diastolic. It was noted that the systolic pressure of several patients in this group was more easily influenced by excitement and exertion than that of normal persons. The blood pressure in patients

of group II corresponded closely to that of other patients with the same types of heart disease.

Electrocardiograms.—One or more electrocardiograms were made of 35 patients of group I. Fifteen of these patients with pure neurocirculatory asthenia had sino-auricular tachycardia ranging in rate from 110 to 160, while one had premature auricular beats producing a bigeminy which reverted to normal rhythm after exercise. Eight patients had diphasic T waves in lead 2 with inverted T waves in lead 3. six obese patients had slight left axis deviation and 5 well developed and well nourished patients had a tendency to right axis deviation. Five patients gave histories of paroxysmal tachycardia. Electrocardiograms taken on one or more occasions of 42 patients of group II showed the usual changes expected for the particular organic heart disease present.

PROGNOSIS

Prognosis in uncomplicated neurocirculatory asthenia is always good so far as length of life is concerned. There is, however, some degree of incapacity, the amount depending on several factors: the severity of the symptoms, the constitutional make-up of the patient and the intensity or adequacy of the treatment. It should be borne in mind that with a return of the causative factors, there will probably be a return of the symptoms, especially in the cases of classes B and C. In the cases of group A, the symptoms often cease permanently after an adequate rest or convalescence.

A group of 601 patients with effort syndrome was studied over a period of five years by Grant ¹¹ in 1925 to determine immediate prognosis of the condition. Of these, 15.3 per cent recovered entirely, 17.8 per cent improved, 56.2 per cent remained stationary and only 2 per cent became worse. The incidence of serious disease in this group was 8.7 per cent; the most frequent infection was tuberculosis (3.7 per cent). Definite heart disease developed in only 1 per cent. As noted by one of us (White, 1931 ¹⁵), there is a distinct tendency for persons with neurocirculatory asthenia to live partially crippled lives.

TREATMENT

The most essential point in the treatment of neurocirculatory asthenia is to take the patient wholly into one's confidence, to explain carefully the nature of the condition, to dispel all fears of heart disease or, if any disease is present, to explain the degree of limitation of activity necessary in view of the organic disease and also to explain that the symptoms are dependent on the neurocirculatory asthenia and not on the heart disease.

15. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

The plan of life of the patients should be worked out with care and understanding. Each patient should realize that he or she must live within certain limitations, in order to avoid things that produce symptoms; these limitations vary in different persons. Usually normal but quiet work and play are advisable, with avoidance of late hours, coffee, tea, overindulgence in alcohol and tobacco, strenuous vacations, excitement in general, too many hours at work and undertaking new and burdensome tasks or duties. Often after a few follow-up visits over a period of a few months, the patient adjusts himself to his surroundings and has no further symptoms. In the more severe cases of groups B and C, either with a marked psychoneurosis or a definite constitutional defect, it may be wise to seek a consultation with a psychiatrist with the hope of clearing up emotional conflicts present. After this has been done it is wise to follow the patient from the cardiac point of view, giving helpful reassurance regarding the heart; psychoanalysis alone will not cure.

Numerous drugs have been tried in the treatment of neurocirculatory asthenia, but for the most part they have been found to be of little value except in very nervous patients for whom mild sedatives such as bromides or the phenobarbital derivatives are often helpful in the symptomatic treatment. Whether or not suprarenal sympathectomy may prove to be of value cannot as yet be stated; Crile¹⁶ has reported good results in several cases.

Re-education and reassurance are the keynotes of treatment. For the more severe cases, however, saturation with rest at the beginning is often advisable, with the prescription of proper rations of rest thereafter. Suitable rationing of rest is to be recommended for all cases.

SUMMARY AND CONCLUSIONS

1. To throw more light on certain aspects of neurocirculatory asthenia (in particular, its etiology and symptoms) we have presented the analysis of 100 cases, 50 without and 50 with organic heart disease.

2. In this series of 100 cases the females outnumbered the males, 69 to 31.

3. The average age of civilian patients is higher than that among soldiers during the war, doubtless because one is dealing with all ages in the community. The ages in our series ranged from 12 to 69 years, the average age for 100 patients being $35\frac{3}{4}$ years ($31\frac{1}{2}$ years for those with pure neurocirculatory asthenia and 40 years for those with complicating organic heart disease).

16. Crile, G. W.: Recurrent Hyperthyroidism, Neurocirculatory Asthenia and Peptic Ulcer: Treatment by Operations on the Suprarenal Sympathetic System, *J. A. M. A.* **97**:1616 (Nov. 28) 1931; Denervation of the Adrenal Glands for Neurocirculatory Asthenia, *Surg., Gynec. & Obst.* **54**:294, 1932.

4. Only 9 per cent of our 100 patients were poorly developed or undernourished. The great majority were well developed and well nourished, or obese.

5. Neurocirculatory asthenia may be classified etiologically:

A (1) That which follows severe infection, operation or other illness (9 per cent of our cases). (2) That following prolonged fatiguing work or heavy strain of some other sort without respite (10 per cent of our cases).

B (1) That following a slight to moderate infection, operation or other illness (25 per cent of our cases). (2) That following a slight to moderate amount of fatiguing work or of strain of any sort (36 per cent of our cases).

C. That occurring after little or no strain, but tending to be much aggravated by illness or fatigue (20 per cent of our cases).

6. The borderline between the normal and the abnormal is ill defined, but it is best indicated by the appearance of symptoms in the course of the usual physical activities and excitements of daily life, which previously gave no symptoms, or which in the average person would produce no symptoms.

7. Neurocirculatory asthenia is to be distinguished from "irritability of the heart" alone as shown by premature beats or paroxysmal tachycardia.

8. It is also to be distinguished from neurosis as such, in which anxiety, hypochondriasis or hysteria is predominant. We have analyzed 25 such cases for comparison.

9. It differs from ordinary neurasthenia, in which the flight into disease is manifested primarily by lack of energy, easy mental and physical exhaustion and irritability. We have presented data with reference to symptoms in 25 cases of neurasthenia.

10. Neurocirculatory asthenia is a term to be preferred to effort syndrome in designating the condition under discussion, since effort syndrome may be produced in normal people.

11. Palpitation, respiratory discomfort, precordial pains or aches and exhaustion are the four cardinal symptoms of neurocirculatory asthenia. They occur in the order named with almost the same frequency (78 to 73 per cent of our 100 cases).

12. Radiation of the precordial discomfort of neurocirculatory asthenia to the left arm, axilla, shoulder or scapula may occur (in 33 of 74 cases of our own). The more severe the precordial discomfort, the more likely the radiation.

13. Sighing respiration and precordial tenderness are important confirmatory signs and are almost pathognomonic of neurocirculatory asthenia.

14. When neurocirculatory asthenia complicates organic heart disease the symptoms are essentially the same in character and quantity as they are in the absence of organic heart disease.

15. The fundamental mechanism of neurocirculatory asthenia remains obscure. Variations of the same mechanism in different persons or, indeed, even different mechanisms may give rise to the different combinations of symptoms and signs.

EXPERIMENTAL POSTOPERATIVE EDEMA

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In a previous communication¹ we discussed the occurrence of generalized edema of the tissues following ordinary surgical procedures. The edema described was observed in a series of thirty-four patients and was of varying degree, but at times amounted to anasarca. In certain instances it proved to be a serious postoperative complication, especially when occurring in the intestinal wall and parenchyma of the lungs. Death apparently resulted from the edema in one case, and it was believed that the swelling of the intestinal wall might have contributed definitely to the malfunctioning of a gastro-enterostomy in several instances. It was thought that the edema was fundamentally of the nutritional type frequently associated with a lowering of the serum protein. Such a lowering of the serum protein below the critical level actually was observed in nearly all the cases. In attempting to explain the occurrence of this interesting phenomenon it was obvious that frequently the associated undernutrition of long standing was of primary importance. It was also evident that other factors were operative which, if not equally important, were nearly as important as the state of actual undernutrition. It appeared, for instance, that in the absence of a considerable fluid intake the serum protein would not drop and the edema would not develop, even though undernutrition was present. In addition, we noted that the daily intake of sodium chloride by various routes was excessive in most of these patients; this was undoubtedly another important factor in the accumulation of fluid in the tissues. In one group of patients with perforated appendixes requiring drainage the element of undernutrition was absent, but the occurrence of generalized edema was no less striking than in others. The important factor appeared to be excessive drainage with con-

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1. Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema, *Arch. Surg.* **27**:159 (July) 1933.

sequent loss of protein or the factor of sepsis, resulting in a generally increased permeability of the capillaries, or a combination of both.

It is our purpose to report the experimental production of post-operative edema. We have attempted to reproduce in animals the actual condition occurring in ordinary surgical procedures on human beings, particularly as related to abdominal surgery. In these experiments we have tried to control and study the effects of variations in diet, fluid intake, nitrogen intake, salt intake, operative shock, drainage and sepsis.

METHODS

Full grown male cats were used in these experiments, and all operative procedures were performed under full surgical anesthesia. The basic diet for normal cats contained 1 Gm. of nitrogen and 72 calories per kilogram of body weight with adequate mineral salts and vitamins. The diet contained the following, per kilogram of body weight:

Casein.....	2.5 Gm.		
Hamburger steak.....	15.0 Gm.		
Liver.....	6.0 Gm.		
Cornstarch.....	3.0 Gm.	Salt Mixture:	
Sugar.....	3.0 Gm.	Sodium chloride.....	10 Gm.
Butter.....	1.1 Gm.	Calcium lactate.....	4 Gm.
Salt mixture.....	0.2 Gm.	Magnesium citrate.....	4 Gm.
Bone ash.....	0.4 Gm.	Ferric citrate.....	1 Gm.
Harris yeast.....	0.1 Gm.	Compound solution of iodine.	2 drops
Cod liver oil.....	5 drops		

The diets containing 0.5, 0.3 and 0.1 Gm. of nitrogen per kilogram of body weight were based on the standard diet with the casein, meat and liver reduced to the correct nitrogen content and the calories maintained by increased carbohydrate and butter content.

Before the cats were placed on the control diet a Ssabanajew-Franck gastrostomy was performed in most instances, so that if they refused to eat their quota of food they could be fed through the gastrostomy opening. The entero-anastomosis, when performed, was made between the upper portion of the jejunum and the lower part of the ileum. The cats were etherized, and the routine surgical technic used on patients was employed. In those experiments in which the production of serous drainage was attempted, a standard cigaret drain was placed in the peritoneal cavity under aseptic precautions. Sometimes the site of the drains became infected after ten days or two weeks, but usually after that length of time the omentum walled off the end of the drain, gradually forcing it out of the wound and causing drainage to cease. In only one cat did peritonitis result, but in several cats an abscess well walled off at the inner end of the drain was found at autopsy.

In producing abscesses the abdominal wall was shaved, and 1 cc. of turpentine was injected subcutaneously. Abscesses formed within three days and usually broke in five days with drainage of thick purulent material. As soon as one abscess started to heal another was produced, so that there was constant loss of drainage material.

Hypodermoclysis consisted of 5 per cent dextrose in water or physiologic solution of sodium chloride. The animals were given approximately the same amounts of fluid per kilogram of body weight as are administered frequently to patients during routine postoperative care.

The cats were kept in specially constructed individual cages so that the urine and stools could be collected separately without loss and be fairly accurately measured. The urine and stools were tested for the nitrogen content according to Kjeldahl's method. Urinary chlorides were determined by Folin's method. The serum protein, albumin and globulin were determined by the method reported by Howe;² the nonprotein nitrogen was determined by Folin's method and the serum chlorides by Fiske's method.

As soon as the cats were killed autopsy was performed. Sections of the heart, lungs, liver, pancreas, kidney, pylorus, midileum, ileum or anastomosis, abdominal wall and leg muscle were weighed immediately and dried to constant weight over a period of from five to seven days, and the percentage of water was calculated. Sections of these tissues were prepared for histologic examination. Each day before receiving the hypodermoclyses the cats were weighed and examined for any evidence of peripheral edema, and the output of urine and the sodium chloride content were measured.

In the protocols the results of the determinations are expressed as follows: serum protein and albumin in grams per hundred cubic centimeters; nonprotein nitrogen and sodium chloride of the blood and urine as milligrams per hundred cubic centimeters; the hemoglobin and hematocrit readings and the water content of the tissues in per cent.

EXPERIMENTAL RESULTS (CONTROL)

A group of control animals was studied in order to obtain figures for comparison with animals subjected to the several procedures. The animals were placed on a diet sufficient to maintain body weight, which contained 1 Gm. of nitrogen per kilogram of body weight and adequate minerals and vitamins for growth. Analyses of the blood (table 1) were made at the end of three weeks, at which time the animals were killed.

Specimens of the various organs were studied for water content as already described, and the results are given in table 2. These figures correspond fairly closely with those obtained by Skelton.³

As a further check on any possible changes that might occur because of variations in the diet alone, for a period of from three to four weeks the animals were placed on the basic diets except that the nitrogen content was 0.5, 0.3 and 0.1 Gm., respectively, per kilogram of body weight. Because there were no changes in the blood of any significance except for a lowered serum protein in cat 14, and because of the absence of any clinical edema, weights of tissues were not determined on any of these animals. Analyses of the blood of these cats at the end of the control period gave the values shown in table 3.

It is of interest that even under conditions of nitrogen deficiency there was no important drop in serum protein at the end of approximately one month.

2. Howe, P.: Determination of Proteins in Blood, *J. Biol. Chem.* **49**:109, 1921.

3. Skelton, H.: Storage of Water by Various Tissues of the Body, *Arch. Int. Med.* **40**:140 (Aug.) 1927.

TABLE 1.—*Blood Analyses in Control Animals*

Cat	Serum Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematoerit, per Cent
42	7.1	4.1	3.0	34	658	85	40
43	8.8	5.3	3.5	32	658	80	41
44	6.9	4.1	2.8	30	650	80	39
45	6.3	4.9	1.4	26	660	80	45
46	7.6	4.7	2.9	30	672	80	38
29*	7.8	4.7	3.1	33	614	80	53
21*	7.0	42	640	90	38
31*	7.9	4.6	3.3	39	660	80	40

* No preliminary period on the weighed diet. The cat has been in the stock-pen on rations of raw meat and liver.

TABLE 2.—*Percentage of Water in Tissues in Normal Animals*

Cat	Heart	Lungs	Liver	Kidney	Pancreas	Pylorus	Mid-ileum	Ileum	Abdominal Wall	Leg Muscles
42	78.1	82.2	74.7	73.4	75.9	78.2	79.1	78.8	78.0	77.2
43	72.0	77.3	73.8	75.0	64.0	77.0	76.7	78.8	67.9	75.8
44	76.9	80.2	75.2	76.7	71.2	78.6	78.7	78.2	75.8	77.0
45	76.6	79.2	72.2	77.0	70.0	77.7	77.4	78.4	76.3	76.2
46	78.8	74.6	76.4	71.8	77.7	78.2	78.0	75.7	76.4
29*	75.3	77.0	75.8	78.4	69.8	75.7	73.7	74.1	72.3	75.7
21*	78.6	77.8	72.2	77.9	69.2	76.0	76.4	71.7	77.0
31*	73.0	76.1	73.8	73.6	70.0	75.6	76.6	75.5	72.3	74.5
26A*	73.9	79.2	75.0	78.0	73.2	81.4	77.5	71.8	75.4

* No preliminary period on the weighed diet. The cat has been in the stock-pen on rations of raw meat and liver.

TABLE 3.—*Blood Analyses in Control Animals on Nitrogen-Deficient Diet**

Cat	Diet	Duration	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo-globin, per Cent	Hemato-erit, per Cent
12	0.5	Initial	5.0	6.8	3.1	33	678	80	58
		3 weeks	3.9	8.4	5.3	40	661	85	55
18	0.3	Initial	2.6						
		3 weeks	2.5	6.4	...	34	702	70	40
		5 weeks	2.6	7.1	3.2	31	690	70	38
13	0.1	Initial	2.5	6.3	3.4	37	658	80	33
		4 weeks	1.9	5.9	4.0	31	673	80	45
14	0.1	Initial	2.5	6.8	3.2	41	690	70	30
		4 weeks	1.9	5.1	3.1	35	702	70	35
27	0.1	4 weeks	2.8	6.9	3.8	31	702	70	35
22	0.1	Initial	2.2						
		3 weeks	1.6	6.8	3.5	24	672	60	24
		4 weeks	1.5	6.5	2.5	30	690	65	28
33	0.1	Initial	3.7						
		4 weeks	3.1	6.6	4.3	20	658	70	33
34	0.1	4 weeks	2.8	6.0	3.9	20	...	70	37
28	0.1	3 weeks	2.4	6.5	3.1	38	614	85	38

* Nitrogen content reduced to 0.5, 0.3 and 0.1 Gm.

I. EXPERIMENTAL RESULTS FOLLOWING HYPODERMOCLYSIS AND VARIATIONS IN DIET

The first group of experiments was carried out in an attempt to determine the effect of hypodermoclysis on the production of edema in animals which received diets respectively adequate and inadequate in nitrogen and in which hypodermoclysis constituted the only source of food. Determinations of the water content of the tissues were not made in all the animals receiving the diet and hypodermoclysis simultaneously. In animals receiving hypodermoclysis only, following a previously known diet, such determinations were made and are shown in the protocols. For several days preceding the period of the experimental weighed diet the animals received the diet of raw meat and liver given in the stock-pen, which contained more than 1 Gm. of nitrogen per kilogram of body weight.

Previous experiments⁴ had already been carried out in an attempt to produce edema in animals with an inadequate nitrogen intake. In several instances these experiments included periods of from three to four months of marked nitrogen starvation and were associated frequently with transient drops in the serum protein and albumin to below the so-called critical level. In no instance did edema develop, and it was concluded that this was due to the fact that the animals were receiving relatively small amounts of fluid a day.

The protocols for the present experiments follow.

A. Effect of Hypodermoclysis Accompanying the Maintenance Diet.—CAT 57.—This animal was given the diet containing 1 Gm. of nitrogen and 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day for thirty-five days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent
Initial.....	3.9	7.2	3.6	37	620	70	36
15.....	4.0	7.6	...	25	643	70	33
35.....	4.7	7.2	4.1	40	588	70	42

The cat thrived on the diet and was well and healthy at the end of the period. The output of urine was normal at all times.

B. Effect of Hypodermoclysis in the Presence of an Inadequate Nitrogen Diet.—CAT 56.—This animal was given the diet containing 0.1 Gm. of nitrogen and 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day for thirty-five days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent
Initial.....	2.5	6.9	3.2	25	665	65	30
15.....	2.3	7.1	...	20	630	65	30
35.....	2.1	7.3	3.6	20	731	65	30

4. Unpublished data.

The cat was well and healthy at the end of the period. The output of urine was normal at all times.

C. Effect of Hypodermoclysis Alone Following a Normal Diet.—CAT 8.—This cat was taken from the stock-pens and given 100 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day. The animal lived only thirty-one days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.8	11.3	4.6	85	672	75	35	104
3	3.6	7.5	4.1	46	690	70	34	83
7	3.3	6.6	4.4	48	660	70	34	57
15	3.0	6.7	4.0	38	660	60	36	60	716
22	2.6	5.8	2.9	27	707	70	33	85	1,079
25	Hypodermoclysis increased to 200 cc. daily								
30	2.3	9.9	4.8	39	602	60	22	110	1,463
31	Cat died							150	2,160

Autopsy revealed nothing abnormal. The cat was very emaciated. The water content of the tissues (per cent) was: ⁵ heart, 80; lungs, 78.3; liver, 68.6; pylorus, 81.6; pancreas, 79.

It is of interest to note the sharp terminal rise in serum protein and serum albumin in the absence of urinary retention. Examination of the water content of the tissues indicated beginning edema in the heart, pylorus and pancreas.

D. Effect of Hypodermoclysis Alone after a Previously Deficient Nitrogen Diet.—CAT 33.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty days; then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in water were substituted for the food. After seventeen days the cat became so weak that it was killed. At that time the front paws, legs and chest were slightly edematous. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.1	6.6	4.3	20	658	70	33
5	2.6	6.3	4.0	26	599	75	30	190	33
11	2.5	6.6	3.9	41	672	60	20	185	111
17	2.4	6.0	3.6	42	544	60	26	100	40

Autopsy revealed the legs and chest to be edematous. The tissue between the skin and the abdominal wall was filled with bubbles of fluid, although there was no excess of fluid in the abdomen. The intestine was large and bluish silver. There was questionable edema of the colon. No fluid was found in the lungs. The heart was flabby, and the pericardium contained a bloody fluid, probably caused by a puncture of the heart to obtain blood. The water content of the tissues (per cent) was: heart, 80.6; lungs, 80.6; liver, 74.4; kidney, 76.3; pancreas, 81.5; pylorus, 80.4; midileum, 79.7; ileum, 80.4; abdominal wall, 76.5; leg muscle, 78.

The histologic report showed very slight edema of the submucosa of the ileum and moderate edema of the interstitial tissue of the pancreas. The leg muscle showed a very slight trace of edema. All other tissues were free from edema.

CAT 27.—This animal was given the diet containing 0.1 Gm. of nitrogen for twenty-one days; then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet. Edema of the paws occurred after

5. Figures of more than 0.5 per cent above the maximum normal control figures are italicized to indicate edema.

eleven days and then disappeared until the fifteenth day, after which it appeared only transiently. The animal was killed because of weakness twenty-three days after the hypodermoclyses were started. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.8	6.9	3.1	32	702	70	35	100	580
8	2.4	6.4	2.7	25	655	70	30	278	2,209
11	2.3	6.0	3.0	25	680	60	20	210	2,100
18	2.0	6.5	3.5	28	614	65	17	280	2,632
23	1.8	7.2	4.9	28	526	65	17	200	1,774

Autopsy revealed edema of the legs only. The intestines were enlarged and very moist, but there were no other abnormalities. The water content of the tissues (per cent) was: heart, 76.5; lungs, 79.3; liver, 75.1; kidney, 79.3; pancreas, 78.4; pylorus, 79.1; midileum, 79.4; ileum, 79.2; abdominal wall, 73.1; leg muscle, 76.8.

The histologic report showed questionable edema of the leg muscle. The lymphatics were slightly prominent in the pylorus, midileum and terminal ileum, but there was no definite edema.

The terminal rise in the values for serum protein and serum albumin in cats 8 and 27 should be noted. These were undoubtedly premortem phenomena such as have been noted frequently by earlier investigators toward the end of experiments with starvation and probably represent a rather rapid dissolution of the tissues.

II. EXPERIMENTAL RESULTS FOLLOWING HYPODERMOCLYSIS AND VARIATIONS IN DIET ASSOCIATED WITH ENTERO-ANASTOMOSIS

A second group of animals was studied with a view to determining the effect of hypodermoclysis when diets of varying nitrogen content are given immediately after an entero-anastomosis. A gastrostomy was performed long before the entero-anastomosis was done, and we were therefore able to vary the food intake at will. The entero-anastomosis was performed between the upper jejunum and terminal ileum, and had the double advantage of allowing us to make observations on animals with a recent intestinal operation and also of interfering with the proper absorption of food because of the short circuit performed on the bowel. With the exception of cat 5 the animals received food during the postoperative period, although, because of the nature of the operation, the actual amount absorbed was not known. In this respect the procedure differed from that in a gastro-intestinal operation on a human being when there is virtual starvation for days. The amounts of fluid given by hypodermoclysis varied between 24 and 66 cc. per kilogram of body weight, which corresponds to between 1.7 and 4.6 liters for a man weighing 70 Kg. At times these amounts were undoubtedly excessive for both fluid and sodium chloride. There is no doubt, however, that not infrequently equivalent amounts have been administered as a routine to dehydrated patients after operation. As

a control experiment four animals were studied for the effect of anastomosis alone without hypodermoclysis. They were followed for periods of a hundred and fifteen, forty, eighteen and fourteen days after the anastomosis was performed. Protocols for these are not given, as edema did not develop.

From the control experiments it is obvious that the prolonged period of undernutrition associated with anastomosis of the jejunum and ileum did not result in the appearance of edema. There was an apparent increase in water in the lung tissue in one animal, but this is the only possible exception, and we cannot offer an explanation for it. Although the diets were adequate in every respect, it is obvious that these animals failed to absorb their food properly, as evidenced by a constant loss of weight. The absence of peripheral edema or edema of the tissues probably can be explained by the fact that the fluid intake was relatively low and no extra salt was administered.

A. Experiment Showing the Effect of Entero-Anastomosis Combined with an Adequate Diet and Hypodermoclysis.—CAT 30.—This animal was given the diet containing 1 Gm. of nitrogen for twenty-five days prior to anastomosis and for twenty-three days afterward, at which time 200 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day was substituted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.4	8.1	4.7	36	614	70	41
9	2.7	7.3	3.8	36	687	70	37	42	50
16	2.7	7.2	3.9	57	681	70	30	57	374
25	2.2	7.3	3.6	58	678	68	280
25	Hypodermoclysis started								
29	2.3	5.1	3.1	60	688	60	27	120	1,200

Autopsy revealed the chest and paws to be edematous. A watery and mucoid stool was passed just before the animal was killed. Between the skin and abdomen there was much fluid and in the abdomen a slight excess of fluid. The lungs contained over 1 cc. of pleural fluid, and there was a slightly bloody fluid in the pericardial sac, probably from a puncture of the heart to get blood. The anastomosis was in perfect condition. The water content of the tissues (per cent) was: heart, 82.5; lungs, 84.1; liver, 75.2; kidney, 82.5; pancreas, 82.9; pylorus, 82.5; midileum, 85.1; anastomosis, 83.6; abdominal wall, 79.5; leg muscle, 78.6.

The histologic report revealed slight edema in the lungs, anastomosis, midileum and pylorus.

Subcutaneous edema was noted only on the day the animal was killed. It is of interest that the appearance of edema and a lowering of the serum protein and serum albumin followed closely to the subcutaneous administration of the salt solution. There was also a slight terminal urinary retention.

B. Experiment Showing the Effect of Entero-Anastomosis Combined with the Diet Containing 0.5 Gm. of Nitrogen and Hypodermoclysis.—CAT. 38.—This animal was given the diet containing 1 Gm. of nitrogen for seven days prior to

anastomosis and the diet containing 0.5 Gm. of nitrogen for three weeks after the anastomosis, when 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis was substituted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.4	6.3	4.4	37	687	80	53	32	288
7	2.0	5.7	3.5	36	672	60	23	30	396
13	1.8	5.8	3.0	46	626	79	25	18	105
20	1.6	5.9	3.0	46	725	60	27	0	0
24	Hypodermoclysis started								
26	1.6	5.1	2.5	46	627	40	520

Two days after hypodermoclysis was started, the cat was killed because of weakness. Autopsy revealed nothing abnormal. The water content of the tissues (per cent) was: heart, 80.1; lungs, 80.1; liver, 75.9; kidney, 80.9; pancreas, 79.1; pylorus, 78.5; midileum, 84.4; ileum, 77.2; abdominal wall, 79.4; leg muscle, 78.5.

The drop in serum protein and serum albumin and the oliguria corresponded in time with the results obtained in cat 30.

C. Experiment Showing the Effect of an Entero-Anastomosis Combined with Hypodermoclysis Alone.—CAT 5.—This animal was given the diet containing 1 Gm. of nitrogen for thirty days prior to anastomosis. After the operation it received 100 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day. The cat lived for twenty-nine days after the operation. Diarrhea was present for seven days preceding death. Edema of the front legs and face appeared two days before death and disappeared on the following day.

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	4.2	10.7	2.9	55	1,070	85	47	55
3	3.8	6.9	3.1	46	681	70	37	75
7	3.4	6.8	3.1	37	702	70	33	50
12	3.0	5.9	2.5	24	673	65	30	80
15	2.9	7.3	2.5	31	672	65	30	83
19	2.7	6.8	3.6	26	674	60	28	75
27	2.3	5.7	3.4	26	655	60	20	20
30	2.1	6.5	2.0	34	707	60	20	93	1,012

At autopsy the skin was juicy, but no fluid was found in any cavity. The heart was flabby, and the lungs were pale. There was questionable edema of the pylorus.

The histologic report revealed slight edema of the abdominal wall, leg muscle, pylorus and midileum. Questionable edema was evident in the submucosa of the anastomosed area of the intestine. The pancreas showed edema of the interstitial tissue. The heart, lungs and liver were normal.

This cat can be compared with cat 8 of the preceding group with the exception of the operation performed at the beginning of the experiment. The cats were approximately the same weight and received the same amount of fluid by hypodermoclysis, without any food by gastrostomy. The operative procedure was apparently associated with a more rapid loss of weight and an earlier appearance of edema, as shown by the watery diarrhea. The obvious edema of the tissue was also greater in cat 5.

D.—Experiment Showing the Effect of an Entero-Anastomosis Combined with a Nitrogen-Free Diet and Hypodermoclysis.—CAT 6.—This animal was given the diet containing 1 Gm. of nitrogen for thirty-three days prior to anastomosis.

which was followed by an adequate caloric diet of carbohydrates alone and a daily hypodermoclysis of 100 cc. of 5 per cent dextrose in saline solution, which was increased to 200 cc. two days before death.

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Ce.
Initial.....	4.0	6.9	4.0	48	637	80	43	82
4.....	3.6	8.4	3.2	52	690	55	18	67
8.....	3.3	5.5	2.8	37	667	55	18	112
11.....	3.1	6.3	3.4	32	672	60	25	70
15.....	3.0	5.7	3.1	38	672	60	25	70
24.....	2.8	5.5	4.5	26	655	60	23	70
30.....	2.4	4.7	3.1	30	643	55	20	240

The cat lived for thirty days after the anastomosis; death was due to intussusception of the intestine 2 inches into the anastomosis from the short-circuited loop. The tip of the intussuscepted loop was gangrenous. Evidently all food went through the anastomosis from the contracted lumen of the short-circuited loop. There was no fluid or edema in the abdomen or pleural cavity on gross inspection. The legs were edematous.

The histologic report revealed congestion in the lungs and liver and moderate edema in the leg muscle. The intestine near the anastomosis showed edema of the submucosa, and the pancreas showed acute and chronic pancreatitis.

This experiment showed the effect of increasing the amounts of fluid on lowering the serum protein and serum albumin. There was a sharp drop in both when the hypodermoclyses were increased from 100 to 200 cc. a day.

E. Experiments Showing the Effect of an Entero-Anastomosis Followed by Hypodermoclyses Alone and Subsequent Administration of Food.—CAT 11.—This animal was taken directly from the stock-pen. An anastomosis was performed, after which the cat received a daily hypodermoclysis of 150 cc. of 5 per cent dextrose in saline solution until the thirteenth day, when the diet containing 0.1 Gm. of nitrogen was added. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Ce.	Urine Sodium Chloride, Mg.
Initial	2.2	6.0	...	30	661	70	35
8	1.7	4.2	2.9	38	702	60	18	165	1,550
14	1.5	5.9	2.4	30	672	60	20	140	1,484
14	0.1 Gm. nitrogen diet started								
22	1.4	4.6	2.1	26	672	50	12	190	2,128
23	1.4	4.3	2.0	35	624	191	2,120

The cat was killed twenty-three days after anastomosis, when edema was noted. The legs were baggy and filled with fluid. The abdomen contained 1 cc. of fluid; the same amount was in the pleural cavity and there was questionable fluid in the pericardium. The lungs were very pale. The water content of the tissues (per cent) was: heart, 78.5; lungs, 87.8; liver, 75.5; kidney, 80.1; pancreas, 78.8; pylorus, 80; anastomosis, 80.2; leg muscle, 78.

CAT. 15.—This animal was taken from the stock-pen and anastomosis was performed. It received 200 cc. of 5 per cent dextrose in saline solution by hypodermoclysis daily until the nineteenth day after the operation when the diet containing 1 Gm. of nitrogen was substituted. Nine days after the operation a stitch abscess developed which broke and drained. The cat did not eat the 1 Gm. nitrogen diet well, so after a few days the diet was changed to meat and liver. Rapid improvement followed. After thirteen days on this diet the cat was put

on the 1 Gm. nitrogen diet again, but it refused to eat and died after two days. The edema disappeared as soon as the hypodermoclyses were discontinued and the protein diet given. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Ce.	Urine Sodium Chloride, Mg.
Initial	3.0	6.1	4.5	42	634	85	45
3	...	6.0	4.3	36	640	70	35	300	2,460
6	2.6	5.8	4.0	33	585	70	30	185	1,646
9	2.3	5.1	3.1	25	655	190	2,164
14	2.2	5.6	3.1	18	702	70	36	224	2,295
	Edema								
20	2.0	4.9	2.7	26	660	60	30	100	1,160
	Hypodermoclysis was stopped; protein food was given; edema disappeared								
33	1.9	7.9	6.7	30	614
37	1.7	8.4	4.6	112	526	65	22

Autopsy revealed the heart and lungs to be normal. The abdomen contained 20 cc. of yellow fluid. The loop of the intestine which had been short-circuited was greatly distended and dark red, owing to a volvulus in its center caused by the mesentery of the anastomosis.

The ascitic fluid contained: total protein, 5.4 Gm.: albumin, 2.4 Gm., and non-protein nitrogen, 144 mg. The water content of the tissues (per cent) was: heart, 76.3; lungs, 76.6; liver, 76.3; kidney, 78.7; pancreas, 78.2; pylorus, 76.5; anastomosis, 78.4; abdominal wall, 77.3; leg muscle, 77.3.

The addition of very small amounts of nitrogen toward the end of the experiments on cat 11 was insufficient to maintain the serum protein at a normal level. Relatively larger amounts of fluid and salt were employed than in preceding animals, and edema occurred a little earlier. In cat 15 the timely administration of a completely adequate diet high in protein caused the disappearance of edema and complete recovery. Death was due to a volvulus. The occurrence of edema in nineteen days may have been hastened by excessive amounts of fluid and salt and also by the presence of sepsis. It is of interest to note the rapid rise in the serum protein and serum albumin as soon as a proper diet was instituted.

III. EXPERIMENTAL RESULTS FOLLOWING DIETARY VARIATIONS, AN ABDOMINAL OPERATION AND THE ADDITION OF SEROUS DRAINAGE

A third group of animals was studied with a view to determining the result of the addition of serous drainage to the previous procedures. The experiments consisted of placing animals on diets of different nitrogen contents over variable periods of time, after which an entero-anastomosis was performed and a drain was placed in the abdomen under aseptic conditions. Hypodermoclyses were administered in the same manner as previously described, but no food was allowed after the entero-anastomosis except for cat 4. It was believed that the additional factor of serous drainage produced by the introduction of a standard cigaret drain in the abdominal cavity might tend to lower the serum protein more rapidly than in the previous experiments and would at least tend toward a more rapid formation of edema. In every instance aseptic precautions were fully carried out during the operation for the entero-anastomosis and for the subsequent insertion of the drain. It was found practically impossible, however, to prevent the development

of a local infection around the drain after an interval of two weeks. In each instance the drainage from the cigaret drain was clear serous fluid for a reasonable number of days. Attempts to measure or collect this fluid were unsatisfactory, but in several instances there was an appreciable amount. Toward the end of the experiment there was an infection around the base of the drain, but with one exception this was completely walled off from the rest of the peritoneal cavity. It did, however, contribute an area of sepsis, so that an additional factor complicated the picture before the cats were killed. Protocols are given in the following section.

A. Experiments Showing the Effect of an Entero-Anastomosis and Drainage, Plus Hypodermoclysis After a Diet Containing 1 Gm. of Nitrogen.—CAT 1.—This animal was given the diet containing 1 Gm. of nitrogen for fifty-seven days prior to anastomosis with insertion of a drain. After the operation 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis daily was substituted for the diet. Diarrhea was present constantly after the operation, and there was a profuse discharge from the drain. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.6	6.3	2.1	43	672	60	42	170
3	90	540
6	2.9	5.6	2.5	41	690	70	30	140	1,148
9	...	4.0	1.3	63	631	..	25	140	1,148

The animal was killed on the ninth day. There was much clear serous fluid oozing from the drain, and the abdomen was filled with ascitic fluid. The intestine was from two to three times the normal size and was filled with a dark brown, watery material. The pleural cavity contained fluid. There was an abscess near the gastrostomy opening which was filled with thick creamy pus, but it was not connected with the abdomen. The ascitic fluid contained: total protein, 0.9 Gm.; albumin, 0.6 Gm.; nonprotein nitrogen, 60 mg., and chlorides, 702 mg. The abdominal wall and anastomosis were the only tissue to show a suggestion of edema. The water content of the tissues (per cent) was: heart, 79.7; lungs, 81.3; liver, 72.7; kidney, 77.3; pancreas, 79.6; pylorus, 80.9; anastomosis, 84.1; leg muscle, 79.1.

CAT 10.—This animal was given the diet containing 1.0 Gm. of nitrogen for eight days prior to anastomosis with a drain. Daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet after the operation. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	4.3	6.7	4.6	45	660	85	48	84	663
3	...	4.5	3.2	43	660
7	3.9	5.0	1.9	37	655	80	32	160	1,688
8	...	4.4	2.2	33	645	65	20	190	1,980

Autopsy revealed a partially walled off abscess around the inner end of the drain. The intestine was normal. Some ascitic fluid was noted. There was no fluid in the pericardial sac or pleural cavity. All the organs were normal in appearance, and the anastomosis was in good condition. The ascitic fluid con-

tained: total protein, 4.5 Gm.; nonprotein nitrogen, 183 mg. The water content of the tissues (per cent) was: heart, 80; lungs, 80; liver, 76.5; kidney, 75.5; pancreas, 68.1; pylorus, 75.4; abdominal wall, 65.3; leg muscle, 73.

The rapid drop in serum protein and serum albumin is to be noted, as well as the absence of urinary retention and edema. The high percentage of water in the area of anastomosis in cat 1 is of interest, and may represent local edema after the operative procedure or possibly an accumulation of fluid occurring after trauma and a lowering of the serum protein.

B. *Experiments on the Effect of an Entero-Anastomosis and Drainage with Hypodermoclysis After a Diet Containing 0.5 Gm. of Nitrogen.*—CAT 12.—This animal was given a diet containing 0.5 Gm. of nitrogen for twenty-one days prior to an anastomosis and insertion of a drain, followed by daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution for fifteen days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	5.0	6.8	3.1	33	680	80	58
Initial	3.9	8.4	5.3	40	661	85	55	47	256
4	3.7	5.8	3.5	35	660	70	40	80	1,056
7	3.6	5.8	2.7	40	672	70	40	230	2,550
11	3.4	5.4	3.4	40	672	70	27	74	1,410
14	3.2	5.5	3.1	26	702	60	25	223	2,750
15	...	6.4	4.0	36	600	275	2,842

The cat was killed on the fifteenth day. Autopsy showed everything normal except an abscess well walled off at the end of the drain. The water content of the tissues (per cent) was: heart, 79.2; lungs, 77.5; liver, 69.4; kidney, 77.5; pancreas, 76.3; pylorus, 80; anastomosis, 76.5; leg muscle, 77.8. There was no evidence of edema.

In spite of free serous drainage and the administration of fairly large amounts of salt solution no edema developed even with a drop in the serum protein to the critical level. It is to be noted that there was no urinary retention.

CAT 4.—This animal was given the diet containing 1 Gm. of nitrogen for seventy-five days, and then the diet containing 0.5 Gm. of nitrogen for eighteen days prior to anastomosis with a drain. After the operation the diet containing 0.1 Gm. of nitrogen and a daily clysis of 200 cc. of 5 per cent dextrose in saline solution were given. There was profuse serous drainage from the abdomen. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	3.1	6.5	3.4	45	690	75	41	42	546
Initial	2.9	7.8	4.2	37	672	75	34	80	512
3	...	6.3	4.0	37	672	190	1,929
6	2.4	5.9	3.5	25	602	65	30	30	468
9	2.4	5.3	3.3	33	678	55	20	268	2,160

The animal was killed nine days after the anastomosis was done. Autopsy showed a slight amount of pus around the drain, which was well walled off by the omentum. About 2 cc. of clear serous fluid was found in the abdomen. The intestine was greatly enlarged and swollen; no fluid was found in the lungs or heart. The water content of the tissues (per cent) was: heart, 79; lungs, 81.7; liver, 74.7; kidney, 76; pancreas, 87.1; pylorus, 87.8; midileum, 81.6; anastomosis, 79.1; abdominal wall, 77.5; leg muscle, 75.1.

Histologic examination showed no evidence of edema.

This experiment is similar to the preceding one, but here the relative amounts of salt solution were much greater than those administered to cat 12, and it is to be noted that the fluid content of the tissues was beginning to rise.

C. Experiments on the Effect of an Entero-Anastomosis and Drainage with Hypodermoclysis After a Diet Containing 0.1 Gm. of Nitrogen.—CAT 13.—This animal was given a diet containing 0.1 Gm. of nitrogen for thirty-one days prior to an anastomosis and insertion of a drain and daily hypodermoclyses of 150 cc. of 5 per cent dextrose in saline solution after the operation. On the second day after the operation the paws, chest and face became edematous. Practically no urine was excreted after the operation. The animal lived for three days and received 450 cc. of fluid. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	2.5	6.3	3.4	37	658	80	33
Initial	1.8	5.8	4.0	30	672	70	45	15	150
1	0	0
2	20	497
3	...	4.3	3.3	35	672	25	490

The animal was killed because it was practically dead. The face, paws, and chest were edematous. No fluid was seen in the abdomen, but there was a slight excess of fluid in the chest. The anastomosis was in good condition. The kidneys were purplish, but the other organs appeared to be normal. The water content of the tissues (per cent) was: heart, 80; lungs, 92.2; liver, 76; kidney, 80; pancreas, 73.2; pylorus, 83; anastomosis, 77; abdominal wall, 82.3; leg muscle, 67.1.

The tissues of the pylorus and pancreas showed the only evidence of edema, which was slight.

CAT 14.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty-one days prior to anastomosis with insertion of a drain and daily hypodermoclyses of 150 cc. of 5 per cent dextrose in saline solution following the operation. The cat lived for two days after the operation, during which time it excreted no urine. It received 300 cc. of fluid by hypodermoclysis. There was much drainage, and edema in the front legs was noted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	2.5	6.8	3.2	40	690	70	30
Initial	1.9	5.1	3.1	35	702	70	38	25	215
2	...	5.8	Dead when blood was taken; no urine since operation						

Autopsy showed the front legs, chest and shoulders bulging with fluid. Three cubic centimeters of ascitic fluid and 2 cc. of pleural fluid were found. The bladder was contracted and contained no urine. In the ascitic fluid the total protein was 6.6 Gm. and the albumin 5 Gm. The pleural fluid contained: total protein, 2.1 Gm.; albumin, 1.3 Gm. The water content of the tissues (per cent) was heart, 80.4; lungs, 84.6; liver, 74.7; kidney, 81.6; pancreas, 67.4; pylorus, 73.5; anastomosis, 73.5; abdominal wall, 75.7; leg muscle, 77.3. The only tissues to show evidence of edema were those of the abdominal wall and the pancreas.

In sharp contrast to the preceding experiments marked peripheral and fairly definite visceral edema occurred within from forty-eight to seventy-two hours after the operation. Drainage was profuse, and there was marked urinary retention of water and salt.

IV. EXPERIMENTS SHOWING THE EFFECTS OF PUS FORMATION ON THE PRODUCTION OF EDEMA

In the following group of animals it was decided to introduce the factor of abscess formation, with and without adequate nutrition, to determine if possible the relationship between a massive outpouring of leukocytes and serum with the subsequent loss of protein and its effect on the production of edema. As previously noted, abscess formation was produced by injection of turpentine subcutaneously. In each instance a large abscess was formed which subsequently broke down and drained profusely.

The experiment on cat 18 fortunately forms an interesting link between the preceding group, in which an attempt was made to study the drainage alone, and this group, in which the effect of a profuse purulent discharge was studied.

CAT 18.—This animal was given the diet containing 0.3 Gm. of nitrogen for thirty-four days before a drain was inserted into the abdomen. Then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet. Subcutaneous injections of turpentine into the abdomen were begun twenty days after the drain was inserted, as at this time the drain had been pushed out and the incision had healed. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.6	7.1	3.2	34	690	70	38
	Drain inserted								
6	2.4	6.7	3.0	25	672	70	38
9	...	5.7	3.1	32	614
13	Edema								
13	2.2	5.8	2.7	27	643	70	33
16	2.1	6.2	2.6	35	655
20	2.0	4.8	2.3	27	643	60	20	220
	Edema gone, drain out and turpentine injected								
23	Edema								
23	1.9	4.9	1.2	20	660	55	18	215	2,021
26	1.5	115	2,150
27	1.8	4.7	2.0	26	643	55	12	200	2,000
28	1.7	265	1,934
29	1.7	187	1,350
30	1.7	4.4	2.2	27	655	45	10	165	1,551

Autopsy revealed the paws and chest to be very edematous. There was no fluid or infection in the abdominal cavity, and everything appeared to be normal. The lungs were very moist, and the pericardial sac contained a large amount of fluid. On analysis the pus from the abscesses showed: total protein, 7.6 Gm.; albumin, 0.65 Gm.; nonprotein nitrogen, 43 mg., and sodium chloride, 482 mg. The water content of the tissues (per cent) was: heart, 82.2; lungs, 84.5; liver, 81.0; kidney, 83.2; pancreas, 78.3; pylorus, 83.5; midileum, 80; ileum, 80.8; abdominal wall, 69.1; leg muscle, 82.7.

There was profuse drainage with the development of definite edema in the legs in twelve days. The edema persisted until the drain was pushed out and the incision healed. Three days after the injections of turpentine were begun, the edema reappeared and increased in amount. There was profuse drainage from the abscesses. Toward the end of the experiment it was noted that when blood

was taken from a vein the cat tended to bleed profusely and that the blood did not clot readily. Death probably occurred from hemorrhage from one of the ear veins.

In view of the preceding experiment the following experiments were planned in order to note the effect of a variation in diet and hypodermoclyses in conjunction with the production of superficial sepsis.

CAT 32.—This animal was given the diet containing 1 Gm. of nitrogen for one day. It had been receiving an adequate diet before that. Subcutaneous injections of turpentine were made into the abdomen. No food or hypodermoclyses were given after the abscesses formed. The cat gradually grew weaker and died, fourteen days after the injections were started. Much thick creamy pus drained from the abscesses. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent
Initial.....	3.4	7.5	3.7	33	672	80	..
5.....	2.9	6.2	2.9	54	655	70	27
10.....	2.4	5.5	3.6	126	555	60	37

Autopsy revealed no fluid in the abdominal, pleural or pericardial cavities. The intestine was filled with bile, and the stomach was greatly distended with gas. The gallbladder was greatly enlarged. The water content of the tissues (per cent) was: heart, 81.3; lungs, 78.9; liver, 77; kidney, 78.9; pancreas, 83.1; pylorus, 82.5; midileum, 81.5; ileum, 81.4; abdominal wall, 76.5; leg muscle, 74.5.

This animal had an adequate diet until the subcutaneous injections of turpentine were given, but thereafter received only water by mouth. In ten days the serum protein dropped to the critical level, with a striking rise in the nonprotein nitrogen. Small amounts of water which could not be accurately measured were taken by mouth. Fourteen days after the first injection of turpentine there was no edema. However, weights of the tissues showed that there was an increase of water in the heart, pancreas, pylorus and ileum. It is probable that gross edema would have developed if the animal had been supplied with sufficient water. The terminal rise in nonprotein nitrogen coincided with a rise in the hematocrit reading and probably represented concentration from dehydration.

CAT 22.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty days prior to the injections of turpentine and continued to receive it after the injections were given. The cat lived for fifteen days after the first injection. It refused to eat seven days after the first injection. Much pus drained from the abscesses. A tabulation of findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent
Initial.....	1.6	6.5	2.5	30	690	65	28
7.....	..	6.5	2.5	33	614	65	22
12.....	1.4	6.8	..	36	693	60	18
15.....	1.1	6.8	3.4	41	565	60	18

The animal was killed because of weakness. Autopsy revealed that the abscess extended down both hindlegs; about 4 cc. of thick, creamy pus was removed. The abdomen and lungs looked normal. The analysis of the pus showed: total protein, 8.1 Gm.; albumin, 4.6 Gm.; nonprotein nitrogen, 120 mg.; chlorides, 437 mg. The water content of the tissues (per cent) was: heart, 76.7; lungs, 82.3; liver, 77; kidney, 76.4; pancreas, 76.8; pylorus, 78.2; midileum, 77.3; ileum, 78.1; abdominal wall, 64.4; leg muscle, 79.2.

The liver revealed central congestion, and the kidneys showed moderate fatty vacuolation of the tubular epithelium.

A factor of undernutrition was present at the beginning of this experiment owing to an insufficient nitrogen diet for the preceding month. The same diet, containing 0.1 Gm. of nitrogen, was continued after the injections of turpentine.

At the end of fifteen days the cat was killed and, as in the preceding experiment, no edema was noted. A determination of the weights of the tissues showed an increase in the fluid content of the pancreas and the leg muscle. As in cat 32, it would seem that the lack of fluid intake was an important factor in the failure to produce edema. There was obviously a marked loss of protein in the drainage material from the abscesses.

CAT 25.—This animal was given the diet containing 1 Gm. of nitrogen for thirty-three days before injections of turpentine were started; then 200 cc. of 5 per cent dextrose in saline solution given daily by hypodermoclysis was added to the diet. The cat ate well, but gradually became weaker. Edema of the paws occurred fifteen days after the first injection of the turpentine. The next day the edema became massive and included all the extremities and shoulders. From this time until death the edema gradually decreased, and the volume of urine excreted increased. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Ce.	Urine Sodium Chloride, Mg.
Initial	4.1	7.5	2.3	30	643	75	36	110	1,540
5	4.1	6.9	3.6	25	655	60	23	205	2,332
8	3.9	6.7	3.2	30	643	70	24	200	2,600
16	4.0	5.3	2.8	30	640	65	20	50	320
18	3.8	305	2,275
19	3.5	6.0	3.0	50	614	55	15	300	2,220

The cat died twenty-one days after the first injection of turpentine. The paws were edematous, and the skin and muscles were very juicy. No fluid was found in the abdominal, pleural or pericardial cavities. There was a large abscess on the abdomen. The water content of the tissues (per cent) was: heart, 80.6; lungs, 81.3; liver, 68.6; kidney, 75.8; pancreas, 78.8; pylorus, 79.2; midileum, 81.9; ileum, 84.3; abdominal wall, 78.6; leg muscle, 79. There was slight edema of the abdominal wall and leg muscle. The liver showed extensive degeneration, and the kidney showed extensive degeneration of the tubular epithelium.

Before receiving the injections of turpentine the animal was given an adequate diet which was supplemented with daily hypodermoclyses after the formation of an abscess. Gross edema developed fifteen days after the initial abscess formed, and associated with this was a striking drop in serum protein. There was also urinary retention associated with the development of the edema, but it is of interest that the excretion of urine increased until there was a positive diuresis at the end of the experiment. Six days after the development of the edema the cat died. At that time the paws were very edematous, and the skin and muscles were juicy. There was no accumulation of fluid in the serous cavities, but the weights of the tissues indicated a definite excess of water in the heart, lungs, ileum and muscles as well as in the subcutaneous tissue. The water content of the liver was extremely low; the liver showed definite degeneration on histologic examination. In some of the animals the liver was pale and revealed slight cellular changes. It is of interest that in this experiment urinary retention played only a transient rôle in the production of edema, and undernutrition probably was a minor factor. The caloric and nitrogen intakes were nearly satisfactory until the death of the animal.

It would seem that sepsis and a relatively large fluid intake were the important factors associated with the drop of the serum protein and the development of the edema. It is impossible to measure the importance of injury to the liver in this respect, but it is highly probable that this also constituted a factor of major importance.

CAT 26.—This animal was given the diet containing 1 Gm. of nitrogen for eighteen days before the injections of turpentine. Daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet after the injections were started. Edema of the paws developed four days after the first injection. The cat lived for twenty-one days after the first injection. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.5	6.0	2.5	35	672	85	37	100	1,120
5	3.1	6.4	3.4	20	555	247	3,952
10	3.3	5.8	3.2	33	643	70	34	74	750
11	2.9	510	5,100
16	2.2	4.3	2.0	43	731	70	41	290	2,376
19	2.2	5.1	2.9	40	585	65	35	150	1,280

The paws and chest were edematous and there was questionable edema of the colon and ileum. From 5 to 10 cc. of ascitic fluid was found in the abdomen, while the lungs, though very moist, contained no definite fluid. The edema reached its peak after seventeen days and then receded until death. The water content of the tissues (per cent) was heart, 82; lungs, 80.8; liver, 79.9; kidney, 78.7; pancreas, 82.5; pylorus, 81.1; midileum, 81.8; ileum, 82.5; abdominal wall, 83.1; leg muscle, 81. There was moderate edema of the leg muscle and the abdominal wall, and the pancreas showed moderate edema of the interstitial tissue.

In this animal peripheral edema developed four days after the first injections of turpentine, and in this respect the results differ from those in most of the preceding experiments. The more rapid development of edema in this instance may be due to the effect of sepsis plus large hypodermoclyses augmented by starvation. It is of interest to note in this connection that edema developed in the face of a definite diuresis before any drop in the serum protein was noted. As the experiment continued there was evidence of diminished urinary activity and a drop in the serum protein and serum albumin to a low level. This coincided with the longest period of most marked edema. As in the preceding case, there was a slight terminal rise in the serum protein and a drop in the serum chlorides. Examination of the tissues showed an increase in the fluid content of the heart, lungs, pancreas, pylorus and ileum as well as of the muscles and subcutaneous tissues.

CAT 34.—This animal was given the diet containing 0.1 Gm. of nitrogen diet for twenty-one days before it received injections of turpentine. Afterward daily hypodermoclyses of 200 cc. of 5 per cent dextrose in water were substituted for the diet. Slight edema of the legs appeared five days after the hypodermoclyses and injections were started. The cat was found dead in the cage eight days after the injections began. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.7	6.0	3.9	20	...	70	37	135	5.8
1	2.7	0	...
2	2.8	6.6	5.0	30	541	75	34	190	9.5
6	2.5	0	...

Autopsy showed an extensive abscess on the abdomen, but no penetration into the abdominal wall. There was no fluid in the abdomen or lungs, but the pericardial sac was filled with a clear yellow fluid. The legs and chest were edematous. The blood serum was icteric. The water content of the tissues (per cent) was: heart, 81; lungs, 81; liver, 79.7; kidney, 78.5; pancreas, 72.4; pylorus, 79.4; mid-ileum, 80.9; ileum, 81.3; abdominal wall, 73.5; leg muscle, 79.

This experiment differed from the others in that the fluid injected contained no sodium chloride. Edema developed five days after the injections of turpentine and the hypodermoclyses were started, the animal having had an insufficient nitrogen diet for three weeks. With the exception of a possible slight increase in the water content of the heart, lungs and ileum and a more than normal amount of fluid in the pericardial sac there was no abnormal accumulation of fluid in the tissues. The total volume of urine was diminished, and anuria was present on two of the last four days of the experiment. Coincidentally there appeared to be a concentration of the blood which kept the serum protein as well as the hemoglobin and the hematocrit values at the normal level. It is probable that more striking retention of fluid would have occurred if the animal had survived. These findings are to be compared with those of the following experiment.

CAT 28.—This animal was on the diet containing 0.1 Gm. of nitrogen for twenty-one days before the injections of turpentine began, after which daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline were substituted for the diet. There was massive edema of all dependent portions of the body thirteen days after the injections were started. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albu- min, Gm.	Non- protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemo- globin, per Cent	Hema- toerit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.3	6.5	3.1	38	614	85	38	100
5	2.3	6.0	3.3	29	590	60	20	270	1,280
12	1.9	5.9	3.6	26	672	55	15	195	1,911
15	1.9	35	511
16	2.0	75	1,095

Autopsy showed edema of the paws, legs and buttocks and a slight excess of fluid in the abdomen and in the lungs. Everything else was normal. The water content of the tissues (per cent) was: heart, 83.4; lungs, 85.1; liver, 81.7; kidney, 83.3; pancreas, 83.5; pylorus, 80.8; ileum, 81.9; abdominal wall, 81.3; leg muscle, 80.3. The abdominal wall and the mucosa of the ileum showed edema. The villi were also edematous.

In this experiment an attempt was made to reproduce the sequence of events in cat 34 with the addition of sodium chloride to the fluid injected. This animal survived fifteen days instead of five, and although edema did not occur until eight days after the injections began, it was more generalized both peripherally and in the tissues. Without exception all tissues were water-logged. Toward the end of the experiment the serum protein was definitely lowered, and there were oliguria and chloride retention. This experiment showed a striking accumulation of fluid in the tissues as a result of undernutrition, pus formation and the administration of somewhat excessive amounts of fluid and sodium chloride.

It is of interest to speculate why edema did not develop more rapidly in cat 28, which received hypodermoclyses of dextrose and saline solution, than in cat 34, which received clyses of dextrose in distilled water. This is in disagreement with most experimental results, but the discrepancy may be due to the fact that anuria

developed in cat 34 almost immediately after the onset of the experiment. Such a disturbance of the renal function undoubtedly contributed to the more rapid formation of edema.

GENERAL COMMENT

From the foregoing experiments it is evident that by various maneuvers we have been able to produce in animals what may be described as a generalized disturbance associated with an abnormally high water content of the tissues. This edema, produced experimentally, involved not only the subcutaneous tissues, but also the muscles of the heart, lungs, pancreas, pylorus, jejunum, ileum, leg muscles, kidneys and liver. In some of the experiments only certain viscera were involved, and as a rule the heart, intestine, kidneys and pancreas were the first to show edema. In addition, free fluid was noted at times in the pleural, pericardial and peritoneal cavities in appreciable amounts. That such abnormal accumulation of fluid in the tissues is associated with other striking physicochemical changes is highly probable, but the scope of the present experiments limited our studies to the demonstration of edema of the tissues. The edema produced in our studies probably represented what is usually classified as nutritional edema, but our results seem to indicate clearly that undernutrition is only one of several important contributory factors.

Of the factors that we were able to control to a fairly satisfactory degree the following may be noted: general nutrition, from the point of view of caloric requirements; the intake of nitrogen, sodium chloride and water, respectively; the absorption of nutritive material from the gastro-intestinal tract; serous drainage; abscess formation, and, to a certain extent, surgical shock following general anesthesia and an abdominal operation. Factors which seemed to be secondary to those listed and which were beyond our control were those related to hepatic and renal insufficiency. The factors that were approximately under our control were those frequently encountered in operative conditions, particularly in those involving operations on the gastro-intestinal tract. For this reason we attempted to vary all of these factors within the limits commonly found in surgical practice.

As was to be expected from previous observations, the factor of undernutrition, and particularly that of nitrogen starvation, was of fundamental importance. It is equally clear that an adequate fluid intake was essential, even in the presence of nitrogen starvation of long standing, before edema would develop. With the exception of the experiments in which the animals were maintained on diets containing only 0.1 Gm. of nitrogen per kilogram of body weight, edema did not develop until after malnutrition was far advanced, provided no other factors were introduced. When the lack of nitrogen was acute, however, water tended

to accumulate in the tissues more rapidly, provided the fluid intake was considerable. It is evident, however, that the administration of somewhat excessive amounts of fluid was not the only important factor, at least under the conditions of our experiments. Excessively large amounts of fluid, amounting to several times the quantities used in our studies, will undoubtedly produce edema rapidly even in the absence of other factors. In the experiment on cat 18, however, we gave daily hypodermoclyses of approximately 80 cc. per kilogram of body weight, or the equivalent of more than 5 liters in a man of average weight. In the presence of deficiency of nitrogen and a fluid intake of such proportions edema did not develop in this animal until other factors such as serous drainage and sepsis were introduced. In this respect the observations of Atkins and White⁶ on the rapid administration of enormous quantities of salt solution to normal and sick animals are of interest. In their studies the slow, continuous intravenous injection of 1,200 cc. of physiologic solution of sodium chloride in healthy cats produced edema of marked degree after ten hours. In an animal suffering from an acute infection a similar maneuver produced a much greater accumulation of fluid in the tissues as indicated by measurements of the water content of the tissues. Such acute experiments, however, bear only a slight analogy to our own, which more nearly approximated actual clinical conditions.

The influence of large amounts of sodium chloride on the production of edema is not strikingly indicated in our experiments, but has already been recognized by numerous investigators. At best it is only one important variable and is probably of little importance unless combined with other factors. In practically all of our animals the level of blood chlorides was usually well above normal and frequently was in the neighborhood of 700 mg. per hundred cubic centimeters. Therefore, there was practically always available an excessive amount of base capable of holding water in the tissues. In a few instances low figures for sodium chloride were obtained, but these were always terminal findings and probably were of little significance in the immediate problem. A study of the electrolyte concentrations in blood and tissues in conditions similar to those produced by us would have been of undoubted interest, but was beyond the scope of our investigation.

Our findings regarding the relation between the level of serum protein and serum albumin and the development of edema are in accord with numerous clinical observations. Undoubtedly there was a much greater tendency toward an abnormal accumulation of fluid in the tissues when the values for serum protein and serum albumin were at or below the so-called critical levels, as determined by Moore and Van

6. Atkins, J., and White, J. C.: Unpublished data.

Slyke.⁷ When the serum protein was in the vicinity of 5.5 per cent or below, or the serum albumin at or below the level of 2.5 per cent, peripheral edema was frequently noted. At such times it was nearly always true that marked undernutrition was present which was associated with the depletion of nitrogen. At times it would appear that a lowering of the serum protein or serum albumin was due merely to the effect of rapid dilution by fairly large amounts of salt solution given subcutaneously, although it is safe to assume that in nearly every instance tissue protein was already markedly depleted. A careful examination of the protocols shows that in numerous instances peripheral edema and visceral edema of marked degree occurred in the presence of normal values for serum protein and albumin. Here again is a factor of variable importance in the production of edema. By itself it is incapable of causing abnormal accumulation of fluid in the tissues.

The importance of serous drainage as a factor in producing edema is strongly suggested by the experimental results. In the group of experiments in which drainage of the peritoneal cavity was instituted this procedure tended to hasten the accumulation of fluid in the tissues. In most of the experiments in this group there was some infection around the end of the drain, but this was certainly a late development and probably played very little part in the picture. In cat 18, however, we were fortunate enough to be able to study the effect of uncomplicated drainage of the peritoneal cavity. Drainage was profuse for a time, and during this period edema developed with an associated lowering of the serum protein to below the critical level. Coincident with a subsidence of drainage and a final removal of the drain, the edema disappeared. The obvious conclusion is that serous drainage contributed to the development of the edema. Attempts to collect the drainage fluid were unsuccessful, but analysis of the ascitic fluid found in three of the animals at autopsy showed protein contents of 0.9, 4.5 and 6.6 per cent, respectively. It seems highly improbable that the actual loss of protein occasioned by drainage of any of the fluids would in itself seriously alter the serum protein content under normal conditions. In association with marked undernutrition, and the administration of moderately large amounts of fluid and salt, it is entirely possible that such a loss of protein was of real importance in the production of edema, probably through a lowering of the serum protein.

The rôle of sepsis seems to be of extreme importance in our experimental results; it appears to explain the occurrence of edema noted in the cases of gangrenous appendicitis previously referred to. Like

7. Moore, N. S., and Van Slyke, D. D.: Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* 8:337, 1929.

all the other factors already mentioned, excessive drainage of purulent material alone would probably be insufficient to produce marked edema, but when combined with the administration of saline solution in sufficient amounts and nitrogen depletion it seemed to be associated with striking results. Even in the absence of large amounts of fluid administered by hypodermoclysis edema of the tissues was demonstrable (cat 32 and 22), and when clyses were given, extensive edema developed. That it could be a determining factor is apparently illustrated in the experiment on cat 18. Here, with a constantly excessive fluid intake and nitrogen starvation edema appeared first with the establishment of serous drainage and disappeared when drainage ceased. It reappeared as massive anasarca when abscess formation was instituted. There are two possible explanations of the effect of abscess formation. The obvious one is that there was a striking and constant loss of nitrogenous material in the pus, with a consequent lowering of the serum protein. Analyses of samples of the purulent material collected from the abscesses gave values as high as 8.1 per cent protein and 4.6 per cent albumin. Especially in conditions of nitrogen starvation the loss of such amounts of protein might well contribute to an already existing nitrogen depletion.

In addition, however, it is interesting to consider the general effects of sepsis, as such. It is possible that there is a constant general reaction of the body to histamine or histamine-like substances in the presence of abscess formations with resulting increased capillary permeability. Under such conditions lack of nitrogen and a somewhat excessive fluid intake might result in a striking accumulation of fluid in the tissues. The increased water content of the tissues noted in the acute experiments already referred to, when animals suffering from an acute infection of the respiratory tract were used, strongly supports such a conception. The rôle of sepsis may therefore be a dual one, combining the factors of loss of protein and increased capillary permeability. It is possible that general anesthesia and surgical procedures may also play an analogous rôle to sepsis by means of transient effects on capillary permeability. Our experiments offer no evidence that this is true, but it is of interest to conjecture on the importance of such a factor in relation to major surgical procedures in badly depleted patients.

In addition to the factors just mentioned two other factors must be noted which undoubtedly played an important part in the production of edema. Urinary retention of water and sodium chloride was noted on many occasions. At times it was a transient phenomenon, and marked edema occurred in several instances when there was excellent diuresis. On the other hand, whenever retention was present, marked edema was usually noted. Complete anuria was noted twice. As a rule, diminished

urinary secretion was noted in association with the greatest degrees of nitrogen depletion. Disturbances of hepatic function could not be measured, but the appearance of the liver at autopsy strongly suggested that there were hepatic changes. Histologically, moderate degrees of necrosis were noted in the livers of several animals in which abscesses had been produced. As the glycogen content of the liver was undoubtedly depleted in practically all of the animals because of starvation, and probably because of sepsis, it is not unreasonable to suppose that normal water balances in the body were somewhat disturbed as a result.

As far as the relative importance of each of these factors in the production of edema is concerned, it is of interest to glance at tables

TABLE 4.—*Findings at the Onset of Edema*

Cat	Initial Diet, Gm. of Nitrogen per Kg. of Body Weight	Procedure Following Initial Diet	Day Edema Was Noted	Daily Hypodermoclyses, Cc. per Kg. of Body Weight	Daily Sodium Chloride, Gm. per Kg. of Body Weight	Blood Chemistry			Urinary Retention
						Serum Protein, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Serum Chlorides, Mg. per 100 Cc.	
30	1.0	Anastomosis	28	60	0.53	5.1	1.9	687	+++
5	1.0	Anastomosis	27	24	0.23	5.7	3.4	655	++
11	1.0	Anastomosis	23	68	0.60	4.3	2.0	624	0
15	1.0	Anastomosis	20	66	0.60	4.9	2.7	660	±
33	0.1	17	64	0.59	6.0	3.6	544	+
25	1.0	Abscess	15	45	0.45	5.3	2.8	640	++
28	0.1	Abscess	13	74	0.66	5.9	3.6	672	+++
18	0.3	Drainage	12	80	0.72	5.8	2.7	654	..
27	0.1	11	64	0.58	5.9	3.0	690	0
34	0.1	Abscess	5	71	0.64	6.6	5.0	541	0
26	1.0	Abscess	4	50	0.45	6.4	3.4	555	0
18	...	Abscess	2	80	0.72	4.9	1.2	660	+
13	0.1	Anastomosis, drainage	2	60	0.54	4.3	3.3	672	++++
14	0.1	Anastomosis, drainage	2	60	0.54	(5.8)	++++

4 and 5. It seems obvious that edema developed most rapidly in those animals in which the most marked depletion of nitrogen was present. When this was combined with sepsis, drainage or an entero-anastomosis, edema occurred with extreme rapidity. The relative amounts of water and salt administered seemed to play a much less important rôle. Interference with the proper absorption of food resulted in the formation of edema only after a much longer period of time. The factor of urinary retention was important but inconstant. The level of serum protein and serum albumin was of importance only at times. The degree of water retention in the tissues also seemed to depend largely on the degree of undernutrition, especially in the presence of sepsis, serous drainage or a recent surgical procedure. Of all the factors nitrogen starvation and sepsis seem the most important, but only when combined with the administration of sufficient fluid and salt.

It is of some interest to consider the possible clinical significance of the edema noted in the various important viscera. Under ordinary

circumstances the term edema is used to denote an abnormal accumulation of fluid in the subcutaneous tissues. Pulmonary edema and effusions into the serous cavities are also recognized clinically. However, one does not ordinarily think of edema as occurring in such organs as the heart, intestines, pancreas and kidneys. Yet our findings give fairly conclusive proof that water can accumulate to a rather striking degree under proper conditions in any of the parenchymatous organs. It is unfortunate that we did not study the brain tissues in the experimental animals, as several showing marked edema elsewhere had convulsions, appeared disoriented and may well have had cerebral edema. The frequency with which an increase in water content was noted in the heart

TABLE 5.—*Findings at Death*

Cat	Initial Diet, Gm. of Nitro- gen per Kg. of Body Weight		Pro- cedure Follow- ing Initial Diet	Day Edema Was Noted	Dura- tion of Life, Days	Daily Hypo- dermo- lyses, Cc. per Kg. of Body Weight	Daily Sodium Chlo- ride, Gm. per Kg. of Body Weight	Blood Chemistry			Uri- nary Reten- tion	Tissue Edema	Periph- eral Edema
	Serum Pro- tein, Gm. per 100 Cc.	Serum Albu- min, Gm. per 100 Cc.						Serum Chlo- rides, Mg. per 100 Cc.					
30	1.0	Anasto- mosis	28	28	60	0.53	5.1	1.9	687	+++	+++	+	
5	1.0	Anasto- mosis	27	29	24	0.23	6.5	1.9	707	0	+	±	
11	1.0	Anasto- mosis	23	23	68	0.60	4.3	2.0	624	++	+	+	
33	0.1	17	17	64	0.59	6.0	3.6	544	+	++	++	
25	1.0	Abseess	15	21	45	0.45	6.0	3.0	614	0	+	+	
28	0.1	Abseess	13	15	74	0.66	5.9	3.6	672	+++	+++	+++	
18	0.3	Drainage abseess	12	31	80	0.72	4.4	2.2	655	0	++	++	
27	0.1	11	23	64	0.58	7.2	4.9	526	0	+	+	
34	0.1	Abseess	5	8	71	0.64	5.8	4.7	450	++++	++	++	
26	1.0	Abseess	4	21	50	0.45	5.1	2.9	585	0	++	+	
13	0.1	Drainage abseess	2	3	60	0.54	4.3	3.3	672	++++	+++	++	
14	0.1	Drainage abseess	2	2	60	0.54	(5.8)	Dead	...	++++	+++	+++	

was striking and, to us, surprising. In many instances the increases were slight, but in several animals they amounted to 4 or 5 per cent and in rare instances to as much as 10 per cent. Such a change represents a marked alteration of the physiology of the tissues, and one wonders seriously whether similar changes in the heart and other viscera may not so alter the functions of these organs as to interfere seriously with homeostasis. Under such conditions the circulatory, urinary, hepatic and digestive systems, for example, may all be somewhat disturbed and, from a lack of correct individual functioning, may fail to coordinate properly among themselves. The diarrhea which occurred in several of the animals, for example, appeared always to be a concomitant of edema of the intestinal tract. With diarrhea all the nutritional processes were manifestly upset, and a vicious circle was at once established. One is led to speculate whether various maneuvers such as the administration of a general anesthetic, surgical operations and the administra-

tion of narcotics may be followed in depleted patients by results utterly different from those obtained in patients in better condition. It is not reasonable to suppose that the cardiorespiratory apparatus, for example, will function normally with an excessive amount of water in the muscles of the heart and lungs. Urinary retention may well be aggravated by the existence of an already edematous kidney. The similarity of the so-called beriberi heart to the condition of edema of the heart muscles in our animals is notable. In other words, from the very existence of conditions such as we have produced in our experimental animals, we can readily conceive of the difficulties which may face the depleted preoperative patient when subjected to any major surgical procedure which necessarily involves further depletion, surgical shock, hypodermoclyses and possible surgical drainage. Obviously measures tending to maintain nutrition must be instituted, and the dangers of flooding the patient with excessive amounts of water and salt must be minimized as much as possible.

SUMMARY AND CONCLUSIONS

1. In a group of animals we have produced experimentally edema of the subcutaneous tissues and the viscera by measures simulating those not infrequently practiced on patients undergoing operations.

2. The production of edema appears to depend on certain factors which we have been able to vary independently. These factors, in the order of importance, seem to be nitrogen starvation, general malnutrition, sepsis, the administration of somewhat excessive amounts of water and sodium chloride, serous drainage, major surgical procedures and general anesthesia. Disturbances of renal and hepatic function play important rôles, but are secondary to the other factors.

3. The lowering of the serum protein and of the serum albumin is of importance in tending to make fluid accumulate in the tissues, but edema can readily occur in the presence of normal values.

4. The abnormal accumulation of water in the solid viscera has been noted and has been discussed in relation to homeostasis.

5. We have discussed the importance of our findings in their clinical application to the problem of the preoperative patient who is a poor risk.

GASTRO-INTESTINAL STUDIES

III. DETERMINATIONS OF ENZYMES ON AUTOPSY SPECIMENS FROM CASES OF PERNICIOUS ANEMIA AND PELLAGRA

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The importance of the deficiency in gastric secretion in the etiology of pernicious anemia has been established by the work of Castle and his associates. It is still a debatable question whether in this disease there is also a disturbance in the external secretory function of the pancreas. Anemia due to pancreatic disease has been sporadically described in the literature.¹

Villa,² on the basis of the determination of fat, protein and trypsin in the feces, concluded that in pernicious anemia, depending on the severity of the disease, there is not only gastric achylia but also intestinal achylia and, in particular, pancreatic achylia. Landau and Glass³ reported nine cases with both gastric and pancreatic achylia; however, they stated that the condition is rare. Cheney and Niemand,⁴ as a result of determining trypsin in the gastric contents after fasting, believed that pancreatic insufficiency might be of etiologic importance in pernicious

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2. Villa, L.: La funzione del pancreas e l'achilia gastroenterica negli stati anemici: criteri diagnostici e dietetici, *Clin. med. ital.* **58**:295 (July-Aug.) 1927.

3. Landau, A., and Glass, J.: Achylia gastro-pancreatici, *Arch. f. Verdauungskr.* **46**:192 (Oct.) 1929.

4. Cheney, G., and Niemand, F.: Possible Relationship of Pancreatic Insufficiency to Addison-Biermer (Pernicious) Anemia, *Arch. Int. Med.* **49**:925 (June) 1932.

anemia. On the other hand, Crohn,⁵ Chace and Meyers,⁶ White⁷ and McClure and Jones⁸ found normal or even increased amounts of pancreatic enzymes in the duodenal contents of the patients with pernicious anemia whom they examined. Fodor and Kunos,⁹ although unable to find a case with pancreatic achylia, reported a decrease in diastase in the duodenal contents of patients with pernicious anemia.

Recently we¹⁰ reported the results of the analyses of the duodenal contents of twenty-two patients with pernicious anemia. In every case pancreatic enzymes were found, although in some instances trypsinogen, especially, was present in decreased amounts. The patients with decreased amounts of trypsinogen showed moderate to advanced involvement of the central nervous system. To secure more data on the rôle of the gastro-intestinal enzymes in pernicious anemia, specimens of gastric and duodenal mucosa and of pancreatic tissue were secured at autopsy from patients who had had pernicious anemia. Since the gastro-intestinal symptoms in pellagra are sometimes similar to those associated with pernicious anemia, specimens were also obtained at autopsy from patients who had had pellagra. As a control specimens were obtained from persons who died of diseases other than pernicious anemia and pellagra and who did not show gastro-intestinal symptoms.

The gastric mucosa was analyzed for pepsin and rennin. The tryptic, lipolytic and amylolytic activity of the pancreatic tissue was estimated. The ability of the duodenal mucosa to activate trypsinogen was also determined.

METHODS

The Determination of Pepsin and Rennin in the Gastric Mucosa.—The gastric mucosa was scraped off with a knife, and a weighed quantity (from 5 to 6 Gm.) was placed in a flask with 50 or 100 cc. of 0.3 per cent hydrochloric acid and allowed to autolyze for three hours at 40 C. (104 F.) in order to activate the pepsinogen.

5. Crohn, B. B.: The Diagnosis of Functional Activity of the Pancreatic Gland by Means of Ferment Analyses of the Duodenal Contents and of the Stools, *Am. J. M. Sc.* **145**:393 (March) 1913; *Studies in Pancreatic Disease*, *Arch. Int. Med.* **15**:581 (April) 1915.

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The contents of the flask were then filtered through paper and the pepsin and rennin determined by the methods described previously.¹¹ The amount of peptic activity in 100 mg. of fresh mucosa was expressed in terms of 1:4,000 pepsin, U. S. P., and similarly the rennin activity of 100 mg. of fresh mucosa was compared to rennin, U. S. P.

The Determination of the Pancreatic Enzymes.—In removing the pancreas from the body, an effort was made to prevent the duodenal mucosa from coming in contact with the pancreatic tissue. The pancreas was then passed through a meat chopper and dehydrated and defatted by means of ice-cold acetone and ether. The mucous membrane of the duodenum was dehydrated and defatted in a similar way.

The lipolytic and amylolytic activity of the dried pancreatic tissue was estimated by the methods developed by McClure, Wetmore and Reynolds.¹² The amount of activity in 10 mg. of dry tissue was expressed in the units used by McClure.

The tryptic activity was determined on the pancreatic tissue before and after activation by enterokinase derived from duodenal mucous membrane of the individual patient examined and from the duodenal mucosa of swine. To activate the trypsinogen, 200 mg. of powdered pancreatic tissue and 100 mg. of powdered duodenal mucosa were weighed into a flask, and 100 cc. of fifteenth-molar phosphate buffer (p_H 7) was added. This mixture was allowed to incubate, with constant stirring, for thirty minutes at 40 C. It was then filtered, and 5 cc. of filtrate, corresponding to 10 mg. of dry pancreatic tissue, was used for the determination of tryptic activity by methods previously described.¹⁰ To determine if the duodenum obtained at autopsy was fully able to activate the trypsinogen, the pancreatic tissue was activated in the same way by means of enterokinase prepared from dehydrated and defatted duodenal mucosa from swine. The tryptic activity of 10 mg. of dry pancreatic tissue was expressed in milligrams of pancreatin, U. S. P.

RESULTS AND COMMENT

The results of the analyses are shown in the table. The absence of proteolytic enzymes in the gastric mucosa obtained from persons who died of pernicious anemia is a logical finding, since neither free hydrochloric acid nor enzymes can be elicited in the gastric secretion of such patients by any known gastric stimulant. These results might also explain why, except in rare instances, pepsin and rennin do not return in the gastric secretion of patients with pernicious anemia even after extensive treatment with liver or stomach preparations.

It was interesting to note that pepsin and rennin were present in the gastric mucosa of the pellagrins, although in smaller quantities than in the mucosa of the controls. The findings in case 6 were particularly significant, in that before death the gastric juice (obtained after stimu-

11. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: *Gastro-Intestinal Studies: I. Gastric Juice in Pernicious Anemia*, J. Clin. Investigation **11**:1129 (Nov.) 1932.

12. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: *New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man*, Arch. Int. Med. **27**:706 (June) 1921.

lation with histamine) showed an absence of pepsin and rennin and was typical of that found in patients with pernicious anemia. It seems likely, therefore, that while histamine stimulation is adequate for the determination of the physiologic function of the stomach in most cases, it is not necessarily an absolute indication of a complete absence of pepsin and rennin in the gastric mucosa. This patient had a normal blood picture, and considering this fact, the presence of pepsin and rennin in the gastric mucosa might indicate that, although there was an absence of pepsin and rennin in the gastric juice, the "intrinsic factor of Castle" might still be present. Castle and his associates¹³ have

*Five Results of Analyses of the Gastric Mucosa for Pepsin and Rennin and the Determination of the Tryptic, Lipolytic and Amylolytic Activity of the Pancreas of Specimens Obtained at Autopsy**

Patient	Age	Diagnosis	Gastric Analysis After Histamine	Pancreas, 10 Mg.					
				Gastric Mucosa, 100 Mg.		Trypsin in Mg. of Pancreatin, U. S. P.			Lipase in Cc. of N/10 Sodium Hydroxide
				Pepsin in Mg. of U. S. P.	Rennin in Mg. of U. S. P.	Before Activation	Activated with Duodenum (Autogenous)	Activated with Hog Duodenum	
1	59	Pernicious anemia	Achylia	0	0	0.8	5.0	4.2	5.9
2	70	Pernicious anemia	Achylia	0	0	0.9	5.4	5.2	1.5
3	52	Pernicious anemia	Achylia	0	0	1.2	5.0	4.5	1.3
4	53	Pellagra	0.6	6	0.6	10.1	9.3	3.3
5	33	Pellagra	0.9	..	1.3	6.6	5.6	1.6
6	57	Pellagra	Achylia	1.0	15	5.4	7.6	7.5	2.9
7	34	Pulmonary embolism	3.8	35	0.4	7.4	8.0	4.0
8	39	Cardiac failure	2.7	22	2.8	4.0	4.0	2.8
9	74	Cardiac failure	1.3	20	2.5	5.5	5.1	1.3

* The specimens examined were obtained from twelve to fifteen hours after death, with the exception of those from case 3, which were obtained thirty-six hours after death.

shown that the "intrinsic factor" was present in four patients with achlorhydria. One had a normal blood picture and the remaining three had a microcytic type of anemia; therefore, the presence of pepsin and rennin does not necessarily mean that the intrinsic factor is always present. However, Wilkinson¹⁴ has shown that in commercial prepara-

13. Castle, W. B.; Heath, C. W., and Strauss, M. B.: IV. Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia; Biologic Assay of Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having no Free Hydrochloric Acid, and of Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *Am. J. M. Sc.* **182**:741 (Dec.) 1931.

14. Wilkinson, J. F.: Activity of Commercial Preparations of Hog's Stomach, *Brit. M. J.* **1**:325 (Feb. 20) 1932.

tions of hog stomach the pepsin content usually parallels the hematopoietic activity. If the pepsin is destroyed, the hematopoietic activity is also lost.

The pancreatic tissue in every case compared favorably in enzymatic activity with pancreatin, U. S. P. Furthermore, the duodenal mucosa obtained at autopsy in every instance was able to activate fully the trypsinogen in the pancreatic tissue. There were no characteristic differences in tryptic, amylolytic or lipolytic activity in the types of cases studied. From these results we conclude that in patients with either pernicious anemia or pellagra the pancreas can form the principal pancreatic enzymes in good quantity, and that the duodenal mucosa can also produce enterokinase to activate the trypsinogen secreted by the pancreas.

CONCLUSIONS

1. The gastric mucosa obtained from three patients with pernicious anemia contained no pepsin or rennin.
2. Pepsin and rennin were present in the gastric mucosa of pellagrins, although in smaller quantities than in persons who died of cardiac failure and pulmonary embolism.
3. The pancreatic tissue from the persons with pernicious anemia and pellagra contained normal amounts of tryptic, amylolytic and lipolytic enzymes as compared with that from persons who had died of cardiac failure and pulmonary embolism.
4. The duodenal mucosa from persons with pernicious anemia and pellagra produced sufficient enterokinase to activate fully the trypsinogen of the pancreatic tissue.

Dr. H. C. Thornton assisted in securing the pathologic specimens.

ORIGIN AND SIGNIFICANCE OF TYROSINURIA IN DISEASE OF THE LIVER

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Disorders in the metabolism of tyrosine are observed in the inborn metabolic anomaly, alkaptonuria, and in so-called tyrosinosis. In the latter condition, tyrosine, dihydroxyphenylalanine, hydroxyphenylpyruvic acid and hydroxyphenyl acetic acid appear in the urine.¹ Tyrosine is occasionally found in the urine in cases of cystinuria.² Tyrosinuria may also occur independently of any anomaly of metabolism. The substance has been recovered in crystalline form from the urine of a normal subject³ and in various pathologic conditions, mainly involving the liver and biliary passages.⁴ The unreliability of the crystalloscopic method of diagnosis was emphasized in a previous communication.⁵

Frerichs and Städeler,⁶ who first demonstrated the presence of leucine and tyrosine in the urine of a patient with acute yellow atrophy of the liver, established the basis for the belief that the amino-acids excreted in the urine in this disease are derived from the decomposition of the liver proteins. In view of the important rôle of the liver in the deamination of amino-acids, a disturbance of this function has also been held responsible for tyrosinuria.

In order to determine the clinical significance of tyrosinuria and to accumulate data which might throw light on its pathogenesis the following points were investigated: (1) the incidence of tyrosinuria in various hepatic and nonhepatic clinical disorders; (2) the amino-acid

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1. Medes, Grace: A Hitherto Undescribed Inborn (?) Error of Metabolism Related to Tyrosine, Abstr., J. Biol. Chem. **87**:XI, 1930; A New Error of Tyrosine Metabolism; Tyrosinosis; The Intermediary Metabolism of Tyrosine and Phenylalanine, Biochem. J. **26**:917, 1932.

2. Abderhalden, E., and Schittenhelm, A.: Ausscheidung von Tyrosin und Leuzin in einem Falle von Cystinurie, Ztschr. f. physiol. Chem. **45**:468, 1905.

3. Rosenbloom, J., and Gardner, W. E.: Tyrosine Crystals in the Urine of a Normal Pregnant Woman, New York M. J. **100**:574, 1900.

4. Bibliography cited by Rosenbloom and Gardner.³

5. Lichtman, S. S., and Sobotka, H.: An Enzymatic Method for the Detection of Tyrosine in Urine, J. Biol. Chem. **85**:261 (Dec.) 1929.

6. Frerichs, F. T., and Städeler, G.: Wien. med. Wchnschr. **4**:465, 1854; Arch. Anat., Physiol. u. wissenschaft. Med., 1856, p. 47.

content of the blood and urine in cases of tyrosinuria; (3) the tolerance for tyrosine as determined by feeding experiments on patients with disease of the liver; (4) the quantitative excretion of tyrosine in the urine, and (5) the relationship of tyrosinuria to jaundice and to the prognosis.

The tyrosinase method of Lichtman and Sobotka⁵ reveals concentrations of 12.5 mg. per hundred cubic centimeters of tyrosine. The advantages of this method over the Frerichs-Städeler crystalloscopic method are economy of time and labor, specificity and sensitivity.

The amino-acid content of the blood and urine was determined by the colorimetric method of Folin.⁷ Folin found that the amino-acid content of normal blood varies between 5 and 8 mg. per hundred cubic centimeters, and that of normal urine between 6 and 20 mg. per hundred cubic centimeters. β -naphthol-sulphonic acid was employed as the color reagent.

OBSERVATIONS

Clinical Incidence of Tyrosinuria.—Fifty specimens of normal urine previously examined by the tyrosinase method gave negative reactions.⁵ The present study also includes observations on one hundred patients with diseases of the liver and bile passages and other conditions in which tyrosinuria has been described. The result of the study is as follows:

	Number of Cases	
	Total	Positive Reaction for Tyrosine
1. Hepatic and gallbladder disease		
Acute yellow atrophy.....	3	3
Subacute yellow atrophy.....	6	3
Catarrhal jaundice.....	12	2
Portal cirrhosis (alcohol), ascites.....	2	0
Portal cirrhosis (alcohol) with superimposed acute degeneration, burns.....	1	1
Cirrhosis of the liver, ascites, syphilis.....	2	2
Toxic cirrhosis (cinchophen).....	7	1
Toxic hepatitis (arsphenamine), syphilis.....	11	2
Cholelithiasis, cholecystitis, cholangitis, chole- docholithiasis	10	2
Malignant disease of the gallbladder, bile pas- sages and liver.....	19	6
Hemochromatosis	1	0
Weil's disease.....	1	0
2. Nonhepatic disease.....	25	1

7. Folin, O.: A New Colorimetric Method for the Determination of the Amino-Acid Nitrogen in Blood, *J. Biol. Chem.* **51**:377, 1922; A Colorimetric Determination of the Amino-Acid in Normal Urine, *ibid.* **51**:393, 1922.

Tyrosinuria occurred in approximately 30 per cent (22 of 75) of the cases of disease of the gallbladder, bile passages and liver. It occurred most frequently in patients suffering from acute and subacute degeneration of the liver and less frequently in patients with malignant disease of the liver and bile passages, obstructive jaundice due to stone, and toxic (from arsphenamine and cinchophen) or catarrhal jaundice.

In cases of pneumonia, leukemia, pernicious anemia and hyperthyroidism the results were negative. Five patients with jaundice complicating pneumonia, heart failure or leukemia had no tyrosine in the urine.

Tyrosinuria might be expected in the presence of extrahepatic parenchymal autolysis. In degenerating carcinoma of the lung tyrosine may be found in the sputum. It may appear in the urine if the degenerating process does not discharge its products through the bronchial tract.⁸ Tyrosine, in amounts of 15 and 25 mg. per hundred cubic centimeters, was demonstrated in the urine of one of eight patients with pulmonary neoplasm studied in this series. Empyema and extensive metastases were also present. The metastases or the lung focus alone, or both, may have been responsible for the tyrosinuria. Metastases to the liver were present in the cases of tumors of the lung with tyrosine crystals in the urine reported by Asperger.⁸

The findings in a case (15) of arsenical dermatitis exfoliativa without icterus or morphologic changes in the liver gave definite evidence of an extrahepatic origin of tyrosinuria in some cases. On three occasions the patient excreted 32, 15, and 17 mg. of tyrosine per hundred cubic centimeters of urine. Despite the absence of jaundice, tests indicated impairment of hepatic function, such as usually accompanies and follows arsphenamine therapy. Some degree of hepatic insufficiency may be a requisite factor in tyrosinuria of extrahepatic origin. Extensive third degree burns may have contributed to the causation of the tyrosinuria in a case (12) of alcoholic portal cirrhosis with recently superimposed acute degeneration of the liver.

The Amino-Acid Content of the Blood and Urine in Cases of Tyrosinuria.—The amino nitrogen content of the blood was determined in seven cases of tyrosinuria. In only a single instance, a case (3) of acute yellow atrophy, was the amino nitrogen elevated (9 mg. per hundred cubic centimeters of blood).

The amino-acid nitrogen content of the urine was determined in six cases. In four, an elevation in the excretion of amino-acids was noted, the highest value being 40 mg. per hundred cubic centimeters (cases 3, 5, 9 and 15). The upper limit of normal excretion is recognized as 20 mg. per hundred cubic centimeters of urine.

8. Asperger, H.: Leuzin und Tyrosin im Harn bei Lungengeschwulsten, Wien. klin. Wchnschr. 43:1273, 1930.

Tyrosine and Amino-Acid Content of the Urine and Amino-Acid Content of the Blood in Tyrosinuria

Case	Patient	Clinical Diagnosis and Result	Date	Tyrosine, Mg. per 100 Cc. of Urine	Amino-Acid Nitrogen, Mg. per 100 Cc.	
					Blood	Urine
1	M. S.	Acute yellow atrophy (necropsy)....	200
2*	Acute yellow atrophy (fatal).....	200 (approx.)
3	Dr. B.	Acute yellow atrophy.....	1/28	25	...	26.5
			1/30	100	9.0	33.0
4	G. P.	Subacute yellow atrophy (necropsy)	4/19	Negative	6.3	12.5
			4/21	Negative	6.1
			4/23	12.5	...	16.5
			4/24	Negative
			4/25	12.5	...	12.5
			6/ 3	Negative
			6/ 6	Negative	...	7.0
					(ante mortem)	
5	R. F.	Subacute yellow atrophy (necropsy)	3/16	Negative
			3/28	12.5	5.6	20.0
			3/30	Negative	...	22.5
			4/ 1	Negative	...	20.0
			4/24	6.5
			5/ 4	7.3
				(ante mortem)		
6	E. W.	Subacute yellow atrophy (necropsy)	10/28	16.5	6.0
			10/30	9.2
			10/31	10.9
7	M. S.	Catarrhal jaundice	11/27	Crystals
			11/30	Negative
8	J. F.	Catarrhal jaundice	1/13	15.0
			1/19	Negative	8.0
9	R. F.	Syphilitic hepatitis (secondary syph- ilis, recovery)	6/16	15.0	6.8	33.0
10	M. B.	Cirrhosis of the liver, ascites, syph- ilis; unchanged	12.5 to 50.0
11	B. McK.	Cirrhosis of the liver, ascites, syph- ilis; unchanged	10/16	16.5
			10/21	30.0	7.3
			11/18	Negative
			2/ 1	Negative
12	J. H.	Portal cirrhosis (alcoholic), ascites, burns, acute degeneration (necropsy)	3/15	25.0
13	L. H.	Arsphenamine jaundice (recovery)...	Crystals
14	Z.	Toxic cirrhosis (cinchophen) (recov- ery)	1/10	15.0
			1/17	Negative
			1/21	12.5
			1/24	Negative
15	S. L.	Dermatitis exfoliativa from arsphen- amine, liver normal (necropsy)	2/10	32.0	...	17.0
			2/15	15.0	...	40.0
			2/17	17.0	...	30.0
			2/19	Negative	...	20.0
16	H. R.	Metastatic carcinoma of liver (ne- cropsy)	20.0 to 25.0
17	M. F.	Carcinoma of pancreas, metastases to liver (clinical)	3/ 4	15.0
			3/ 7	Negative
18	M. S.	Carcinoma of pancreas, metastases to liver (laparotomy)	3/18	15.0
19	C.	Carcinoma of cystic duct, metas- tases to liver (necropsy)	3/ 8	15.0
			3/10	Negative
20	H. S.	Carcinoma of lung, empyema, me- tastases to liver (necropsy)	1/14	15.0
			1/19	25.0
21	J. S.	Carcinoma of ampulla, metastases to liver (laparotomy); fatal	3/15	15.0
22	S. F.	Choledocholithiasis (laparotomy); recovery	3/31	15.0
			4/ 2	15.0
			4/ 7	Negative
23	S.	Postcholecystectomy choledocholith- iasis (laparotomy); unchanged	4/ 4	25.0
			4/ 7	Negative

* Compare data with those of Schützén and Riess.²

Two cases of subacute yellow atrophy with tyrosinuria showed a normal amino nitrogen content of the blood and urine.

The values for tyrosine are expressed in milligrams of amino nitrogen per hundred cubic centimeters. As tyrosine has 8 per cent of nitrogen, from 12.5 to 30 mg. of this single amino-acid per hundred cubic centimeters of urine would not appreciably elevate the total amino nitrogen content of the urine. The increased urinary amino nitrogen in the cases of slight tyrosinuria must therefore be due to the excretion of amino-acids other than tyrosine.

The findings in the cases of subacute yellow atrophy with transient minimal tyrosinuria suggest that tyrosine may constitute as much as one tenth of the amino nitrogen content of the urine. The share of tyrosine in the total amino-acids of normal urine must be considerably lower. In a case (3) of acute yellow atrophy the tyrosine nitrogen content of the urine constituted approximately one fourth of the total output of amino nitrogen.

Tyrosine Tolerance.—Tolerance for tyrosine was tested by administration of 2 Gm. of tyrosine in 100 cc. of hot water to each of three normal subjects. The urine collected in the following four hours contained no tyrosine. The same amount of tyrosine was fed to five patients with disease of the liver. All gave negative reactions. (These were cases of jaundice complicating pneumonia, arsenical hepatitis, toxic cirrhosis ascribed to cinchophen, stone in the common duct and subacute yellow atrophy in a child.) Thirty grams of a mixture consisting chiefly of monosodium glutamate was added to 2 Gm. of tyrosine and fed in 200 cc. of cold tomato juice to each of four subjects, one normal and three with jaundice. Of the latter, two had subacute yellow atrophy with a fatal outcome, and one had a stone in the common duct.

In only one case of subacute yellow atrophy (case 4) did the test give a positive reaction. Two grams of tyrosine fed to this patient did not produce tyrosinuria. One week later a test meal of 30 Gm. of the monosodium glutamate mixture and 2 Gm. of tyrosine fed to the same subject yielded 15 mg. of tyrosine per hundred cubic centimeters of urine collected in the following two hours and 12.5 mg. per hundred cubic centimeters in the urine collected in the succeeding two hours, suggesting the possibility of a diminished tolerance for this amino-acid in this type of hepatic disease.

Frequency of Occurrence and Quantitative Excretion of Tyrosine.—Tyrosine was found in the urine of three patients with acute yellow atrophy. Of twelve examinations of the urine in three cases of subacute yellow atrophy four revealed tyrosine. Of twenty-one examinations made in nineteen cases with malignant condition involving the liver,

seven gave positive reactions for tyrosine. Five of the six tests for tyrosine on two patients with extrahepatic foci of autolysis, in the skin and lung respectively, proved positive.

Except in cases of acute yellow atrophy minimal or moderate amounts of tyrosine, from 12.5 to 30 mg. per hundred cubic centimeters of urine, are excreted. Larger amounts are excreted only in acute yellow atrophy. In case 1, more than 1 Gm. of tyrosine was excreted in twelve hours, and in case 3, 0.9 mg. was excreted in twenty-four hours ante mortem. Death occurred on the fifth day of illness in an early stage of acute atrophy of the liver. In case 2 qualitative observations alone could be made. The intensity of the formation of melanin in the tyrosinase reaction, however, approximated that of case 1.

The inconstancy with which tyrosine crystals have previously been found in the urine in genuine cases of acute yellow atrophy of the liver is due to the limitations of the crystalloscopic method. With the tyrosinase method tyrosinuria is a constant finding in this disease. Its rapid course and rarity render it difficult to collect a large number of repeated observations. In subacute yellow atrophy, on the other hand, the more protracted course permits repeated tests. As the tyrosinuria in the subacute disease is slight, transient frequent tests must be made, or the tyrosinuria may be missed. This probably explains the negative findings in three cases of subacute yellow atrophy in this series, one fatal and one with recovery, in which only single examinations were made.

Relationship of Tyrosinuria to Jaundice and to Prognosis.—Jaundice was present in nineteen of twenty-three cases of tyrosinuria. In two of the four nonjaundiced patients extensive extrahepatic foci of autolysis were present, a carcinoma of the lung in case 20 and an extensive sloughing exfoliating dermatitis due to arsphenamine in case 15. Tyrosinuria was demonstrated in case 18 when obstructive jaundice due to malignancy had been completely relieved by cholecystogastrostomy. Tyrosine was present in the urine on two occasions in a case (14) of toxic cirrhosis ascribed to the action of cinchophen. A transitory icterus had entirely receded.

Eight of twenty-three patients with tyrosine in the urine (cases 7, 8, 9, 10, 11, 13, 14 and 22) recovered or remained in unchanged bodily condition. In all these instances, only minimal or moderate amounts of tyrosine were present in the urine.

COMMENT

The recovery of tyrosine from urine has been considered an ominous sign since the original observation of Frerichs and Städeler in a fatal case of acute yellow atrophy. Schultzen and Reiss⁹ and I have recov-

9. Schültze, N. O., and Reiss, L.: Ueber akute Phosphorvergiftung und akute Leberatrophie, Ann. d. Char.-Krankenh. 15:1, 1869.

ered massive amounts of tyrosine varying from 0.9 to over 2 Gm. from the urine in a period of twenty-four hours in acute cases of the disease. Massive excretion apparently indicates an acute diffuse degeneration of the liver. The excretion of tyrosine is continuous throughout the brief course of this illness.

On the other hand, temporary tyrosinuria, usually slight in amount, does not preclude recovery. In case 11, that of a patient with cirrhosis of the liver and syphilis, tyrosinuria accompanied massive ascites. An acute degenerative process was superimposed on an old cirrhotic lesion. Tyrosinuria vanished with the ascites. Similar observations have been made by Risak,¹⁰ Geronne¹¹ and Hamne¹² in cases of degeneration of the liver. Patients with slight transitory tyrosinuria who recovered, suffered from hepatitis of syphilitic or arsenical origin, toxic cirrhosis, catarrhal jaundice or common duct stone. In subacute atrophy of the liver minimal or moderate tyrosinuria may cease, though the patient may eventually die of functional insufficiency of the liver.

In acute yellow atrophy the amounts of amino-acids lost in the urine are too large to be accounted for by functional impairment. My observations on tyrosinuria support the conception of Frerichs and the findings of Wells¹³ and of Stadie and Van Slyke¹⁴ who suggested that the abnormal amounts of amino-acids lost in the urine in acute yellow atrophy originate mainly from autolysis of liver tissue rather than from impairment of liver function. The normal amino nitrogen content of the blood and urine in some cases of minimal tyrosinuria (cases 4 and 5) furthermore indicates that the latter factor may be insignificant.

Röhmman,¹⁵ who was unable to recover tyrosine from the urine of a patient with acute atrophy of the liver, maintained that amino-acids are excreted only when the rate of their formation exceeds that of their destruction in the body. Schültzen and Riess⁹ and Rohmann isolated a deamination product of tyrosine, oxymandelic acid, from the urine in some patients with tyrosinuria. Minkowski¹⁶ also believed

10. Risak, E.: Ueber das Vorkommen von Leuzin und Tyrosin im Harn, *Med. Klin.* **26**:666, 1930.

11. Geronne, A.: Zur Pathogenese einiger Formen des Ikterus, *Klin. Wchnschr.* **1**:828, 1922.

12. Hamne, B.: Die prognostische Bedeutung positiver Tyrosin und Leuzin Reaktion im Harn bei Hepatitis, *Upsala läkaref.-förh.* **38**:8, 1932.

13. Wells, H. G.: The Chemistry of the Liver in Acute Yellow Atrophy, *J. Exper. Med.* **9**:627, 1907.

14. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, *Arch. Int. Med.* **25**:693 (June) 1920.

15. Röhmman, F.: Chemische Untersuchung von Harn und Leber bei einem Falle von akuten Leberatrophie, *Berl. klin. Wchnschr.* **25**:861, 1888.

16. Minkowski: Krankheiten der Leber und der Gallenwege, in von Merings, J.: *Lehrbuch der inneren Medizin*, Jena, Gustav Fischer, 1919, vol. 11, p. 645.

that the appearance of tyrosine in the urine depended on the rate of the degenerative process in the liver. The present quantitative observations with the tyrosinase method lend some support to this view.

It is clinically significant that tyrosinuria may occur occasionally in patients with long-standing obstruction of the common duct due to stone. Minimal amounts of tyrosine were excreted in the urine in case 22 on two occasions. Obstructive jaundice had existed for eight weeks. The patient was afebrile. The liver was swollen. There was no cholangitis. Following cholecystectomy recovery was uneventful. Geronne¹¹ cited a similar instance of jaundice due to stone in the common duct with tyrosine crystals in the urine.

SUMMARY

Tyrosinuria was studied in health and in disease by the tyrosinase method. Its occurrence and estimation proved to be of significance in the diagnosis and prognosis of diseases of the liver and bile passages and in the interpretation of its mode of origin.

The quantitative observations in excretion of tyrosine confirm the view that the abnormal amounts of amino-acids excreted in the urine of patients with acute atrophy of the liver originate mainly from autolyzed liver tissue. While it is conceded that in acute diffuse degeneration of the liver the function of the liver in deamination may fail and contribute to the amino-aciduria, this factor plays only a minor rôle. Studies of the amino nitrogen content of the blood and urine in some cases of subacute atrophy of the liver with tyrosinuria indicates that in this less acute form of degeneration of the liver tyrosine may appear in the urine when there is no apparent disturbance in the metabolism of amino-acids.

Observations on the rate of excretion of tyrosine are of diagnostic significance. Continuous massive tyrosinuria occurs only in cases of acute yellow atrophy with a rapid and fulminant course. Transitory minimal and moderate tyrosinuria occurs in cases of subacute atrophy of the liver, in degenerating neoplasm of the liver, in toxic degeneration of the liver and uncommonly in obstructive jaundice of long standing due to stone. Inflammatory lesions of the bile passages do not of themselves give rise to tyrosinuria.

Extrahepatic foci of autolysis, such as degenerating tumors of the lung or extensive sloughs of the skin, may give rise to minimal or moderate amounts of tyrosine in the urine.

The transitory nature of minimal or moderate tyrosinuria is demonstrated by repeated tests. During the phase of recovery from degeneration of the liver, the products of parenchymal autolysis have already been absorbed, and tyrosine vanishes from the urine, but with a fresh

attack of degeneration of the liver, tyrosine reappears in the urine. In the stage of repair, namely in coarse nodular cirrhosis, or in the terminal stages of subacute yellow atrophy with a critical reduction in the functioning parenchyma of the liver, tyrosine may not be demonstrable in the urine.

Tyrosinuria may occur without jaundice either in cases of extra-hepatic origin or in those of demonstrable disease of the liver.

Quantitative observations with respect to tyrosine are of prognostic value. In cases of minimal tyrosinuria the patients are more likely to recover, whereas cases of massive tyrosinuria terminate fatally in a short time. Mounting tyrosinuria indicates rapidly progressive degeneration of the liver. However, the absence of tyrosinuria in cases of degeneration of the liver does not warrant an optimistic prognosis.

EFFECT OF TOXEMIA ON TOLERANCE FOR DEXTROSE AND ON THE ACTION OF INSULIN

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In a previous article,¹ attention was directed to the effect of toxemia on the tolerance for dextrose. Rabbits were given injections of varying doses of diphtheria toxin, and daily dextrose tolerance tests were made, 5 gm. of dextrose being used. It was shown that, as the toxemia increased from day to day, the tolerance for dextrose decreased. Some of the animals that survived as many as seven or eight days of the toxemia acquired blood sugar levels as high as 400 or 500 mg. two hours following the administration of dextrose. The exact explanation of this phenomenon is not clear. It may be observed in normal human beings who are toxic,² but is more strikingly seen in diabetic persons who are victims of infections. One of two explanations may be offered for such an effect on dextrose tolerance: (a) an increased glycogenolysis or (b) an inhibition of glycogenesis.

Lawrence and Buckley³ suggested from similar experiments that glycogenolysis is activated through a thyro-suprarenal stimulation resulting from the toxemia. The second explanation seems to us to be more likely. This may occur in one of several ways: by a neutralization or inactivation of insulin by the toxemia; by some disturbance in the natural storehouses of glycogen; by a diminished oxidation of sugar; by a suppression of endogenous production of insulin, or by some combination of them.

A second study⁴ was made in an effort to substantiate one of these views. Rabbits were intoxicated as in the first series of observations

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1. Sweeney, J. S., and Lackey, H. W.: The Effect of Toxemia on Tolerance for Dextrose, *Arch. Int. Med.* **41**:257 (Feb.) 1928.

2. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, *Arch. Int. Med.* **50**:801 (Dec.) 1932.

3. Lawrence, R. D., and Buckley, O. B.: Inhibition of Insulin Action by Toxaemias and Its Explanation: Effect of Diphtheria Toxin on Blood-Sugar and Insulin Action in Rabbits, *Brit. J. Exper. Med.* **8**:1 (Feb.) 1927.

4. Sweeney, J. S.: Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, *Arch. Int. Med.* **41**:420 (March) 1928.

mentioned, and as the toxemia increased from day to day, a uniform dose of insulin was given (2 units) ten minutes after the daily administration of dextrose. We thought that a constant 2 unit effect of insulin

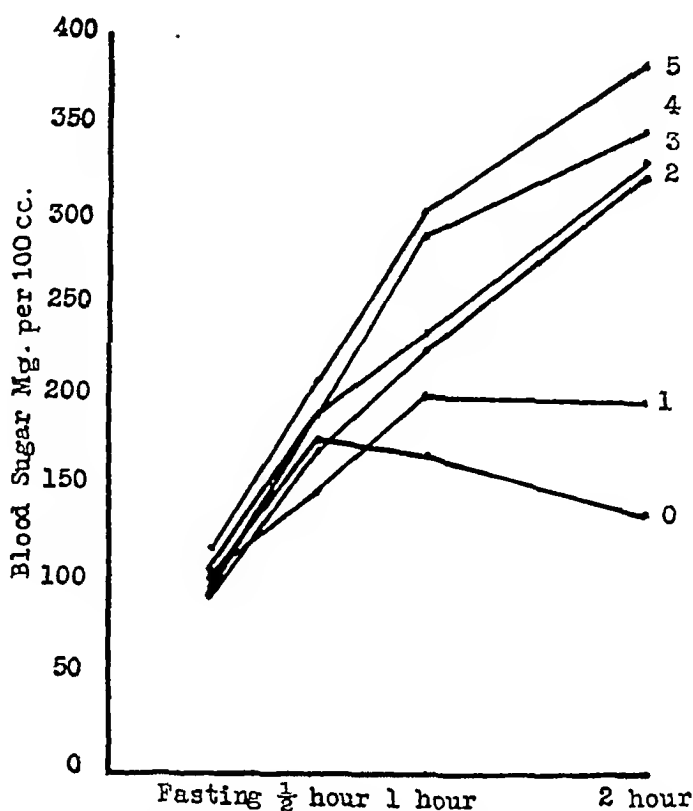


Chart 1.—Daily curves showing the tolerance for dextrose of rabbit 7 following a subcutaneous injection of 0.0075 cc. of diphtheria toxin (the minimum lethal dose equals 0.03 cc.). The numbers at the end of each curve indicate the day of toxemia.

TABLE 1.—Results of Daily Tests of Tolerance for Dextrose of Rabbit 7, Following the Subcutaneous Injection of 0.0075 cc. of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 Cc.)

Hours of Starvation	Hours of Toxemia	Rectal Temperature, F.	Blood Sugar, Mg. per 100 Cc.			
			Fasting	After Dextrose, Min.		
				30	60	120
24	..	105	105	182	179	145
48	24	105	107	152	206	206
72	48	102	95	174	230	333
96	72	101	100	190	244	345
120	96	103	109	190	296	357
144	120	103	120	215	313	400

could be demonstrated, even as the toxemia increased, and it was suggested on the basis of these experiments that the effect of toxemia is that of a suppression of endogenous insulin.

The experiments to be reported in this study are similar to those just mentioned and were performed in an effort to get a better under-

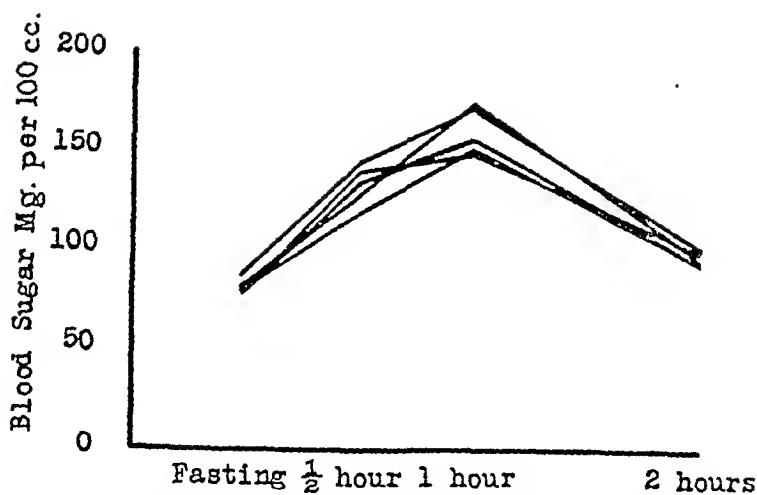


Chart 2.—Daily curves showing the tolerance for dextrose of rabbit D. Neither diphtheria toxin nor insulin was given (table 2).

TABLE 2.—Results of Daily Tests of Tolerance for Dextrose of Rabbit D *

Hours of Fasting	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
24	None	83	131	179	101
48	None	82	123	154	100
72	None	80	140	158	100
96	None	80	143	152	105
120	None	88	148	175	107

* This rabbit received neither diphtheria toxin nor insulin (control). Five grams of dextrose was given daily.

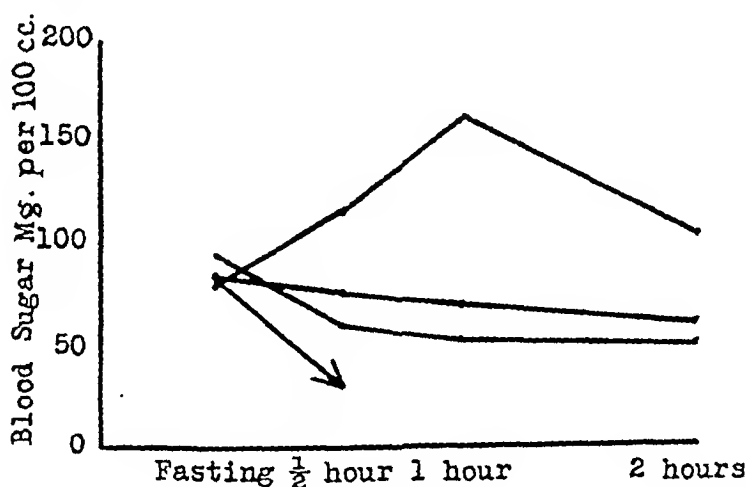


Chart 3.—Daily curves showing the tolerance for dextrose of rabbit A. No diphtheria toxin was given. Insulin in increasing doses (2 units) daily was given twenty minutes before 5 Gm. of dextrose was administered. The animal died in convulsions on the third day following the administration of 6 units of insulin (table 3).

TABLE 3.—Results of Daily Tests of Tolerance for Dextrose of Rabbit A *

Hours of Fasting	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
24	0	80	117	165	105
48	2	87	77	71	60
72	4	83	63	57	51
96	6	87	Died in convulsions		

* This rabbit was given no diphtheria toxin, but daily increased doses of insulin were given twenty minutes before the daily administration of 5 Gm. of dextrose.

standing of the effect of toxemia on the action of insulin. Knowing that the tolerance for dextrose progressively diminishes as toxemia increases, and believing that exogenous insulin is not neutralized by the toxemia, we thought that by giving graduated doses of insulin preceding the administration of dextrose the tolerance curves could be kept normal. This fact would lend weight to the explanation suggested.

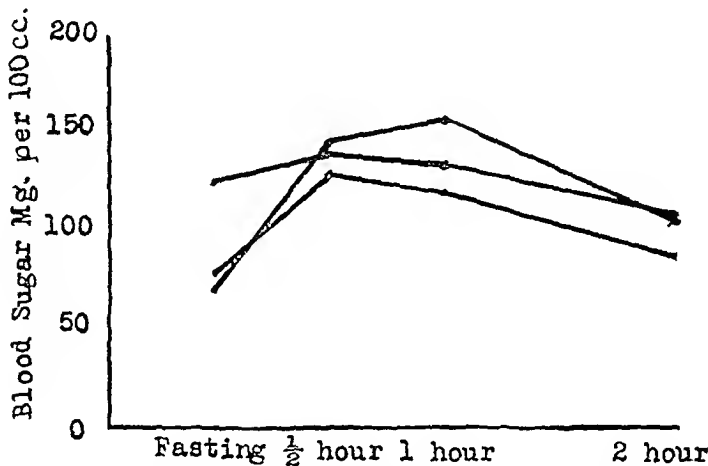


Chart 4.—Daily curves showing the tolerance for dextrose of rabbit E. The animal survived two days following the injection of 0.004 cc. of diphtheria toxin and was given 2 and 4 units on the first and second days of toxemia twenty minutes preceding the administration of 5 Gm. of dextrose (table 4).

TABLE 4.—Results of Daily Tests of Tolerance for Dextrose of Rabbit E*

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Ce.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	73	146	159	104
24	2	85	136	120	94
48	4	125	143	133	105

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

Rabbits were used in the experiment. Food was withheld except after the tests and then removed within a few hours' time. Water was kept in the cages of the animals. Tolerance tests were made of all of the animals for a few days to establish controls. They then received injections of diphtheria toxin, the doses varying from 0.005 to 0.0025 cc. (minimum lethal dose, 0.02 cc.).⁵ Arbitrarily following the first twenty-four hours of toxemia, 2 units of insulin was given twenty minutes before the dextrose was administered. This dose was again arbitrarily

5. The Eli Lilly Company furnished the diphtheria toxin and insulin used in this experiment.

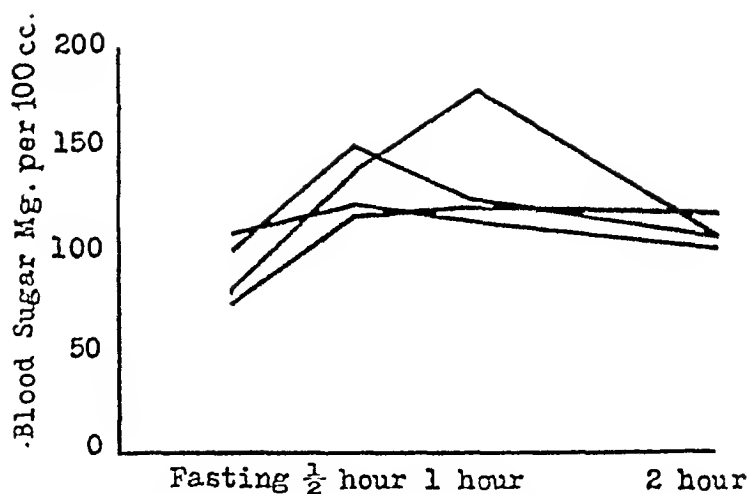


Chart 5.—Daily tolerance curves for dextrose of rabbit F. The animal was given 0.004 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 5).

TABLE 5.—Results of Daily Tests of Tolerance for Dextrose of Rabbit F *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	88	143	182	108
24	2	102	151	128	106
48	4	111	125	118	103
72	6	83	118	125	121

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose 0.62 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

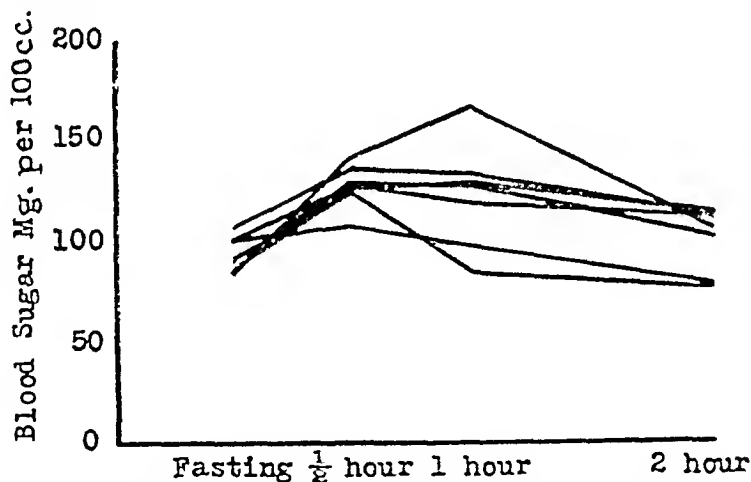


Chart 6.—Daily tolerance curves for dextrose of rabbit G. The animal received 0.005 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 6).

TABLE 6.—Results of Daily Tests of Tolerance for Dextrose of Rabbit G *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	83	143	175	109
24	2	87	138	125	100
48	4	89	125	85	76
72	6	100	111	95	80
96	8	84	120	119	118
120	10	100	131	120	107
144	12	111	140	112	111

* This animal was given 0.005 cc. of diphtheria toxin (minimum lethal dose, 0.6 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

increased 2 units daily and given each time twenty minutes preceding the dextrose. In view of previous tests performed on toxic but non-insulinized animals, no such controls were made in this series of observations. Table 1 and chart 1 are reproduced to illustrate the effect of toxemia on the tolerance for dextrose.

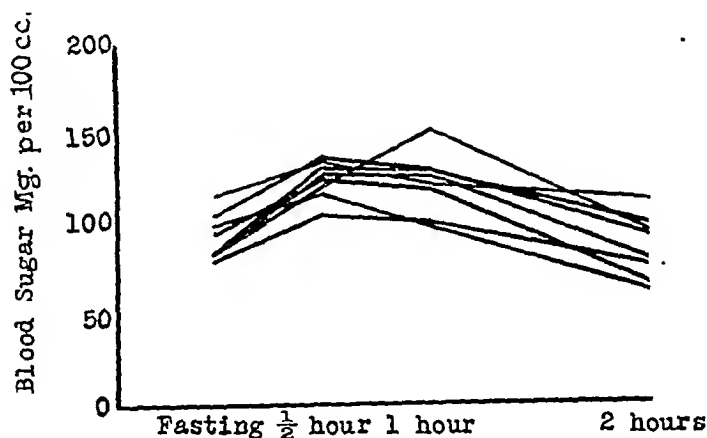


Chart 7.—Daily tolerance curves for dextrose of rabbit H. The animal received 0.0025 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 7).

TABLE 7.—Results of Daily Tests of Tolerance for Dextrose of Rabbit H *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	89	123	154	92
24	2	90	133	129	85
48	4	83	111	100	80
72	6	95	129	120	70.
96	8	100	118	100	67
120	10	111	143	133	93
144	12	89	131	131	100
168	14	118	135	125	118

* This animal was given 0.0025 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

The two groups studied were: (a) nontoxic rabbits that were given subcutaneously daily 2 unit increments of insulin twenty minutes before 5 Gm. of dextrose was administered by stomach tube; (b) toxic rabbits (they had received different dosages of diphtheria toxin, see the tables) that were given subcutaneously daily 2 unit increments of insulin twenty minutes before 5 Gm. of dextrose was administered by stomach tube. In both groups, the blood sugar after fasting was determined and insulin was injected; twenty minutes afterward dextrose was administered, and at thirty, sixty, ninety and one hundred and twenty minute intervals following the administration of dextrose, blood was collected from the

marginal ear veins for an estimation of the blood sugar. The blood sugar was estimated according to the Folin-Wu method. As stated earlier, table 1 and chart 1 are reproduced from a previous study to show in rabbits the effect of toxemia on the tolerance for dextrose without insulin. Table 2 and chart 2 are presented to show the dextrose tolerance curves for a nontoxic and noninsulinized rabbit and table 3

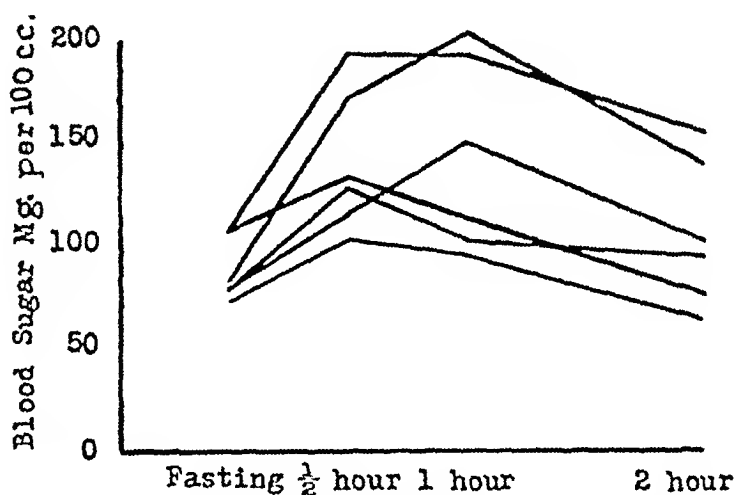


Chart 8.—Daily tolerance curves for dextrose of rabbit B. The animal received 0.004 cc. of diphtheria toxin. No insulin was injected on the first two days of toxemia. On the last three days, daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 8).

TABLE 8.—Results of Daily Tests of Tolerance for Dextrose on Rabbit B *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	80	118	152	107
24	0	83	174	211	143
48	0	111	191	191	167
72	6	111	123	118	83
96	8	83	123	105	95
120	10	77	105	95	69

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). No insulin was given the first two days of toxemia. During the last three days the insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

and chart 3 to show the results of increasing doses of insulin in a nontoxic rabbit. It will be observed that the animal was unable to tolerate 6 units of insulin given twenty minutes before 5 Gm. of dextrose was administered; in fact, two hours after the administration of 4 units the animal showed symptoms suggestive of an impending convulsion.

Table 4 and chart 4 present the figures and curves for another rabbit, E, that received 0.004 cc. of diphtheria toxin, which apparently caused its death during the third day of toxemia. Table 5 and chart 5

contain figures and curves for rabbit F that lived into the fifth day of toxemia following 0.004 cc. of diphtheria toxin. Following the injection of 6 units of insulin on the fourth day of toxemia, the sugar tolerance curve was normal, or even might be called one of increased tolerance.

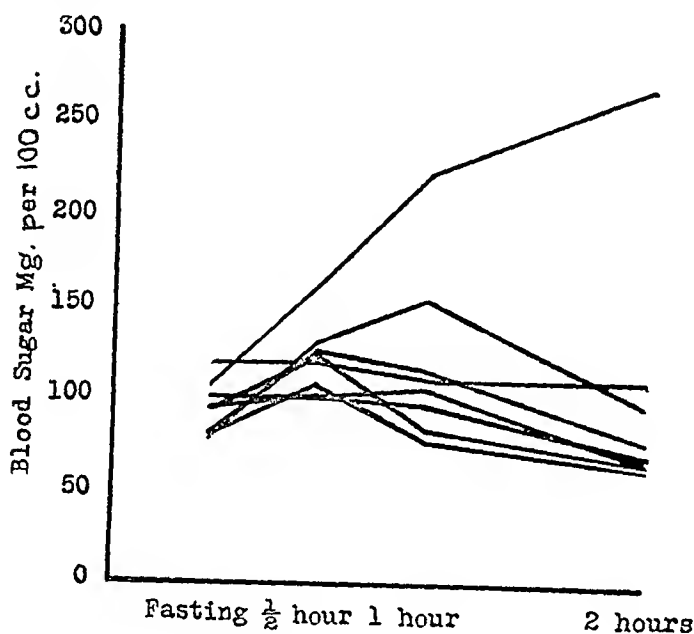


Chart 9.—Daily tolerance curves for dextrose on rabbit C. The animal received 0.004 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given, except on the sixth day. Note the high curve (table 9).

TABLE 9.—Results of Daily Tests of Tolerance for Dextrose of Rabbit C *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
		Fasting	After Dextrose, Min.		
			30	60	120
0	0	80	133	153	93
24	2	83	129	120	80
48	4	80	111	77	65
72	6	91	125	85	67
96	8	100	100	95	70
120	10	90	100	105	67
144	0	111	167	222	267
168	12	118	118	111	111

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). On the sixth day of toxemia, insulin was omitted. On the other days, it was injected each time twenty minutes before the 5 Gm. of dextrose was given.

Rabbit G (table 6 and chart 6) was given 0.005 cc. of diphtheria toxin and survived six days, receiving on the last day 12 units of insulin twenty minutes before 5 Gm. of dextrose was administered. The tolerance curve was normal. In table 7 and chart 7 are the figures for rabbit H that received 0.0025 cc. of toxin, survived seven days and received on the last day 14 units of insulin. The dextrose tolerance curve was again normal.

Rabbit B (table 8 and chart 8) received 0.004 cc. of diphtheria toxin and lived five days. The first two days of toxemia no insulin was given preceding the administration of dextrose. The previously observed diminishing ability to remove dextrose from the blood may be observed. On the third day, however, 6 units of insulin was given as in the previous tests, then 8 and 10 units on the second and subsequent days of life, with resultant normal curves. Rabbit C (table 9 and chart 9), which received 0.004 cc. of diphtheria toxin, lived seven days. As a matter of interest, since the curves were like those for all other toxic rabbits, it was decided to omit insulin on the sixth day of toxemia. A rather sharply rising blood sugar curve was recorded, reaching a two hour level of 267 mg. On the following and last day of the rabbit's life, it was given 12 units of insulin before the dextrose was administered, and a practically level curve was recorded.

Section of the pancreas from toxic rabbit H, which survived seven days of toxemia, was studied by Dr. S. A. Wallace. The glandular epithelium was deeply stained, and the cytoplasm appeared swollen and granular in places. The islands of Langerhans varied in size and, in some of the islands, part of the cells were swollen, with a slightly granular cytoplasm. Many of the islands showed no definite change.

COMMENT

The explanation of these phenomena is difficult. That toxemia diminishes dextrose tolerance largely through thyrosuprarenal stimulation and glycogenolysis is difficult to accept. If such were the case, the blood sugar level after fasting would tend to increase from day to day, which it does not consistently do. It would likewise appear that there is something more than simply suppression of endogenous insulin. In fact, with such fairly large doses of insulin as the rabbits received in relation to the comparatively small quantity of dextrose administered, it would appear as though the animals were totally diabetic so far as exogenous insulin and administered dextrose are concerned. If our accepted ratio of 1 unit of insulin to 2 to 3 Gm. of dextrose is correct, and clinically and experimentally it is, then the only conclusion to be drawn from these observations is that toxemia interferes in some way with the function of insulin, whether the insulin is from an endogenous or an exogenous source. Further work is in progress that has been designed to aid in understanding the mechanism of the effect of toxemia on the tolerance for dextrose and the action of insulin.

SUMMARY

Reference is made to previous experiments showing the effect of toxemia on the tolerance for dextrose. In the present study, dextrose tolerance tests were performed on rabbits intoxicated with varying

doses of diphtheria toxin on successive days of their toxemia. Daily increased doses of insulin were injected subcutaneously twenty minutes before a constant quantity (5 Gm.) of dextrose was given. In this way, the tolerance curves consistently were kept within normal limits. As many as 12 or 14 units of insulin was given on the latter days of toxemia, with the result that the postprandial blood sugar readings continued to be within normal limits.

The only conclusion drawn is that toxemia in some way interferes with the function of insulin whether it is endogenous or exogenous in origin.

NOTE.—Mr. R. Rosenthal, senior medical student, assisted in these experiments.
531 Medical Arts Building.

SALMONELLA SUIPESTIFER BACTEREMIA WITH ACUTE ENDOCARDITIS

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AND

S. LEON ISRAEL, M.D.

PHILADELPHIA

Salmonella suipestifer is seldom encountered in the study of human disease, in spite of its close relationship with the typhoid and paratyphoid bacilli. For some time after knowledge of its association with the virus of hog cholera was recognized, bacteriologists waged a controversy as to its pathogenicity for man. In recent years, especially since the World War, there has been conclusive evidence of its specific relationship to some forms of human disease. During the war, there appeared reports from southern Europe and Asia Minor of epidemics of gastro-enteritis caused by a bacillus resembling that of paratyphoid fever, which was subsequently named the paratyphoid C bacillus. These epidemics were of brief duration and mild in character; especially noteworthy were those reported by MacAdam¹ in Mesopotamia and by Hirschfeld² in Serbia. A few years later, TenBroeck³ and Andrewes and Neave⁴ (working independently) identified this paratyphoid C bacillus as a member of the *S. suipestifer* family, and as giving reactions similar to those of the group I type. Shortly afterward, Savage and White,⁵ using the Lister Institute's national collection of type cultures, recognized several cultures previously reported as paratyphoid C as really being *S. suipestifer* (footnote, table 1). They concluded that this organism was of low virulence and that it could produce human infection

From the Mount Sinai Hospital, Philadelphia.

Read before the Section on General Medicine, College of Physicians, Philadelphia, May 22, 1933.

1. MacAdam, William: An Account of an Infection in Mesopotamia Due to a Bacillus of the Gaertner-Paratyphoid Group, *J. Roy. Army M. Corps* **33**:140, 1919.

2. Hirschfeld, L.: A New Germ of Paratyphoid, *Lancet* **1**:296 (Feb. 22) 1919.

3. TenBroeck, C.: Bacilli of the Hog-Cholera Group (*Bacillus Cholerae Suis*) in Man, *J. Exper. Med.* **32**:33 (July) 1920.

4. Andrewes, F. W., and Neave, S.: Nature and Systematic Position of *B. Paratyphosus C.*, *Brit. J. Exper. Path.* **2**:157 (Aug. 21) 1921.

5. Savage, W. G., and White, P. B.: An Investigation of the *Salmonella* Group, with Special Reference to Food Poisoning, Medical Research Council, Special Report Series, no. 91, London, His Majesty's Stationery Office, 1925.

only under extraordinary circumstances. Following this bacteriologic pathfinding, many observers began to report epidemics of gastro-enteritis with the presence of *S. suipestifer* in the stools. Krumweide, Provost and Cooper⁶ described an outbreak caused by eating tapioca pudding; Cown⁷ reported several cases among travelers coming from areas in which "intestinal grip" was prevalent; Schnitter⁸ and Braun and Mündel⁹ recorded an outbreak in 103 persons who attended a picnic; Savage and White⁵ mentioned the infection of a family, apparently caused by cheese; Scott¹⁰ reviewed five distinct epidemics over a period of a year in England, each caused by infected meat; Stewart and Litterer¹¹ reported an epidemic of 150 cases, supposedly from raw milk. All of these were from food infections, and acute gastro-enteritis was the usual clinical picture.

Following the recognition of the *suipestifer* enteritides, there began to appear sporadic reports of *suipestifer* bacteremias, accompanied by varied clinical syndromes, sometimes suggestive of typhoid fever and at other times of influenza of the "septic type." We have listed these reported cases of bacteremias chronologically (table 1), a total of 34; in each of these, the bacillus was found in the blood in pure culture with the exception of the case reported by Nabarro and White,¹² in which it was recovered from a synovial sac. We wish to add another case to this group of infections due to *S. suipestifer* and to report, at the same time, the appearance of endocarditis during the height of the bacteremia.

REPORT OF A CASE

T. M., a white boy, aged 4 years, was admitted to the hospital on March 15, 1933, having been ill for five days with fever, anorexia, vomiting, prostration and vague abdominal pain. The past medical and family histories were irrelevant. The

6. Krumweide, C.; Provost, D. J., and Cooper, G. M.: Studies on the Paratyphoid-Enteritides Group: Enteric Infection ("Food Poisoning") Due to Tapioca Pudding Contaminated with *B. Cholerae Suis* (*B. Suipestifer*), *J. M. Research* **43**:53 (Jan.-March) 1922.

7. Cown, E. W.: Intestinal Influenza and *B. Suipestifer*, *J. A. M. A.* **86**:58 (Jan. 2) 1926.

8. Schnitter, W.: Zur Epidemiologie und Klinik der Bacillus-Suipestifer-Erkrankungen des Menschen, München. med. Wchnschr. **74**:1011 (June 17) 1927.

9. Braun, H., and Mündel, F.: Ueber den Erreger der Offenbacher Speiseeis-Epidemie, *Klin. Wchnschr.* **6**:1286 (July 2) 1927.

10. Scott, W. M.: The "Thompson" Type of *Salmonella*, *J. Hyg.* **25**:398 (Nov. 26) 1926.

11. Stewart, H. C., and Litterer, William: Outbreak of Gastro-Enteritis; Milk-Borne Epidemic of Dyersburg, Tenn., Caused by *Salmonella Suipestifer*, *J. A. M. A.* **89**:1584 (Nov. 5) 1927.

12. Nabarro, D.; White, P. B.; Dyke, S. C., and Scott, W. M.: Two Cases of Human Infection by American Hog-Cholera Bacillus, *Lancet* **2**:868 (Oct. 26) 1929.

illness started rather precipitately, with frontal headache and a sharp rise in temperature which remained constantly high (from 104 to 105.5 F.). There was a gross and irregular erythema over the trunk and arms for twenty-four hours; there was no sore throat. Persistent vomiting, marked prostration and a gradually

TABLE 1.—*Salmonella Suipestifer Bacteremias*

Year	Authors	Number of Cases		Ultimate Course		Symptomatology
		Adults	Children	Recovered	Died	
1919	*MacAdam ¹	7	..	5	2	Mild typhoid fever and lobar pneumonia
1920	*Dudgeon and Urquhart: Lancet 2: 15, 1920	..	1	1	..	Mild typhoid fever
1921	*Andrewes and Neave ⁴	1	..	1	..	Influenza with pleural effusion and pyuria
1922	MacKenzie: J. Roy. Army M. Corps 39: 51, 1922	1	..	1	..	Infection of upper respiratory tract
1923	*Wordley: Brit. M. J. 2: 105, 1923	..	1	1	..	Bronchopneumonia
1924	Duncan: J. Hyg. 22: 402, 1924	1	..	1	..	Mild typhoid fever
1925	Kopp: Deutsche med. Wehnsehr. 52: 2156, 1926	1	..	1	..	Mild typhoid fever
1926	Shaw: J. Lab. & Clin. Med. 12: 141, 1926	1	1	Severe bronchopneumonia
1927	†Hicks and Robertson: China M. J. 41: 789, 1927	1	1	Typhoid fever
1928	Bullowa: M. Clin. North America 12: 691, 1928	1	1	Severe bronchopneumonia
1929	Bauer and McClintock: J. Infect. Dis. 44: 292, 1929	1	1	Mild typhoid fever
1929	Nabarro and White ¹²	1	1	..	Chronic arthritis
1929	Dyke and Scott ¹²	1	1	Mild typhoid fever
1930	Branham, Motyea and Devine: J. A. M. A. 94: 1758 (May 31) 1931	1	1	Severe infection of upper respiratory tract
1931	TenBroeck, Li and Yu: J. Exper. Med. 53: 307, 1931	4	1	3	2 (ad.)	Paratyphoid fever
1932	Rau: Ztschr. f. Kinderh. 52: 510, 1932	..	1	..	1	Severe gastro-enteritis
1932	Kuttner and Zepp: Bull. Johns Hopkins Hosp. 51: 373, 1932	..	7	7	..	Fever, abdominal pain and vomiting
1932	Haynes, quoted by Kuttner and Zepp	..	1	1	..	Paratyphoid fever
1933	Gouley and Israel.....	..	1	1	..	Mild typhoid fever and endocarditis
	Totals.....	21	14	24	11	(Only 1 of 11 deaths in a child)

* Cases reported as infections with paratyphoid C, but organism was later shown to be *S. suipestifer*.

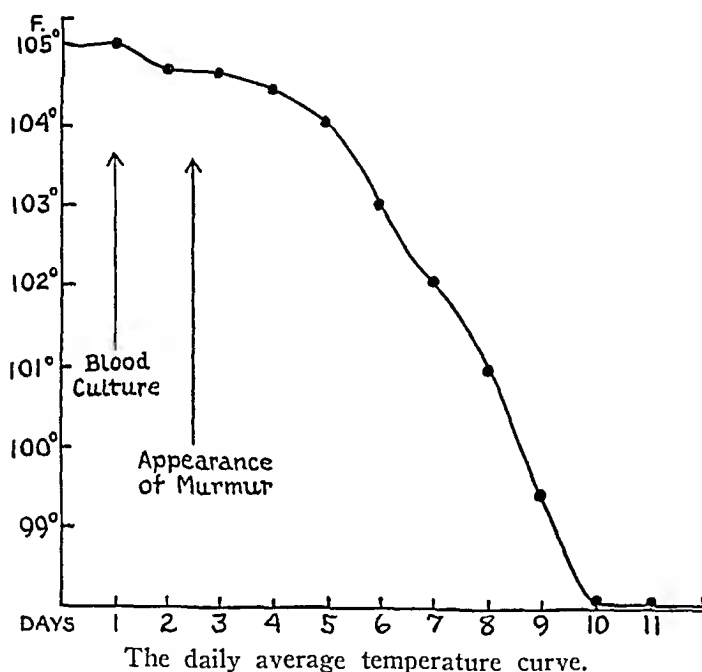
† Case reported as infection with paratyphoid C, but organism reacted like *S. suipestifer*.

increasing abdominal distention suggested the presence of primary peritonitis. On admission, the child's condition was extremely toxic. The temperature was 105 F., the pulse rate 140 and the respiratory rate 38. The heart and lungs exhibited no abnormalities, nor was there evidence of meningeal irritation; the abdomen was generally resistant and tender. The blood chemistry, the icterus index and the results of urinalyses and study of the cerebrospinal fluid were all within normal

limits; the Wassermann reaction was negative. The white blood cell count was 10,000, with 68 per cent polymorphonuclear cells.

Twenty-four hours after admission, the patient's abdomen was softer and he retained fluids administered orally. The hyperpyrexia persisted, as did the marked apathy; the leukocyte count fell to 7,600, with 65 per cent polymorphonuclear cells. A blood culture taken at this time became positive four days later. The spleen was now palpable.

Forty-eight hours after admission, a state of cardiac embarrassment developed, with marked tachycardia and cyanosis of the lips and finger tips. A sharp, rough, high pitched murmur was heard over the precordium, being most intense at the apex and transmitted to the back and axilla; at the same time, signs of pulmonary consolidation developed over the upper lobe of the right lung. The leukocyte count was 8,100, with 79 per cent polymorphonuclear cells.



The Widal reaction was negative, and examination of the excreta for typhoid and paratyphoid bacilli gave negative results. A roentgenogram of the sinuses and chest revealed clouding of the ethmoid cells and incomplete consolidation of the upper lobe of the right lung. On the following day, the fourth day of hospitalization, a double aortic murmur appeared, and the pneumonic signs were less convincing. The temperature began to decline and, on the twelfth day of the illness, became normal (chart). The symptoms entirely disappeared, but the murmurs in both the mitral and the aortic area persisted. The patient left the hospital with a normal temperature on March 26, 1933. He has been under the care of one of us since that time, and there has been no recurrence of fever or any other untoward symptom; the mitral murmur persists, while the aortic murmur has lately disappeared.

The organism which grew in the blood culture broth, after four days of incubation, was a small, motile, gram-negative bacillus. With the aid of Dr. George Walter McCoy at the National Institute of Health

and of Dr. Carl TenBroeck of the Rockefeller Foundation, this bacillus was identified as *S. suipestifer* (probably group I variety). It formed acid in litmus milk, which became alkaline forty-eight hours later. Known suipestifer serum agglutinated it, as did the serum of the so-called paratyphoid C bacillus, and the fermentation reactions were typical of *S. suipestifer*.

The morphologic, cultural and serologic characteristics of *S. suipestifer* are those shown in table 2. In addition, it has a peculiar virulence for rabbit tissues, so that a culture may be transferred to the peritoneal cavity of a rabbit for further study. As a final diagnostic test, it is well to try to agglutinate the organism with some of the patient's serum some months after the original infection, at which time the titer should be high.

TABLE 2.—*Fermentation Reactions of Salmonella Suipestifer*

Acid and Gas	Acid	No Fermentation
Galactose	Xylose	Arabinose
Dextrose	Glycerol	Inosite
Levulose		Trehalose
Maltose		Dulcitate *
Mannose		Lactose
Mannitol		
Rhamnose		

* Irregular and delayed acid formation occurred after twenty days.

COMMENT

The symptomatology of infection due to *S. suipestifer* readily divides itself into three groups: gastro-enteric, pulmonic and septic. A review of the 34 cases of bacteremia previously reported shows a predominance of adults and males. Age appears to be an important prognostic factor. There is an interesting difference in the morbidity and the mortality in the various age groups. The bacteremia apparently pursues a more violent course and has a higher mortality in adults; 21 of the 35 persons were adults and of these 12 died, a mortality of 57 per cent. There were 14 cases in children, of whom only 1 died, a mortality of 7 per cent.

The gastro-enteric form is the most common and often tends to mimic typhoid or paratyphoid fever. It ushers itself in rather suddenly with nausea and vomiting, abdominal discomfort and occasionally diarrhea. The abdominal discomfort is worthy of comment, inasmuch as two children of the reported series underwent fruitless laparotomies for apparent perforations of the appendix. In our case, the abdomen was tender and increasingly tense for the first few days, so that a diagnosis of primary peritonitis was entertained. The next most frequent syndrome, seen especially in children, is the so-called influenzal form, with vague myalgia, drowsiness, chills and hyperpyrexia without any localizing signs. This is often followed by pulmonary complications.

The highest mortality in the adult series obtained in cases with pneumonia. It is interesting to note that in the case reported here symptoms of all three groups were present: nausea, vomiting, abdominal pain, fleeting pneumonia and hyperpyrexia with drowsiness.

Cardiac changes have never been noted. No instance of endocarditis appears in the entire list of cases with *S. suispestifer* bacteremia; furthermore, it is a well known fact that endocarditis is a rare complication in the broad group of typhoid, paratyphoid and allied infections. That this endocardiac lesion was produced by the *S. suispestifer* may only be conjectured, but it is suggested by the fact that the murmurs appeared at the height of the bacteremia and persisted after it and by the fact that the child had never before presented evidence of valvular endocarditis. We are aware of the ease with which functional murmurs develop in children; the factor of cardiac dilatation had to be considered and probably did accentuate the murmurs. We believe at the present time, however, that the murmurs that developed at the height of the acute infection almost certainly represented organic lesions; the peculiar quality of the murmur, the fact that an aortic murmur was heard shortly after the appearance of the mitral murmur, and their persistence long after convalescence suggest that a definite endocarditis had developed. However, since this is the only case reported in which endocarditis developed during the course of *S. suispestifer* bacteremia, it is essential to think of other possible explanations, such as rheumatic fever. The presence of transient pneumonia coincidental with acute endocarditis in a child would be suggestive of a virulent rheumatic infection. If this were the case, *S. suispestifer* would have to be considered a secondary or, at best, a coincidental invader from the gastro-intestinal tract. However, the clinical course, aside from the endocardiac involvement, was not suggestive of a rheumatic infection, even though the features of acute rheumatism are remarkably protean. A review of the case makes a diagnosis of rheumatic endocarditis improbable in the light of the following factors:

1. The tendency to leukopenia, or at least the absence of leukocytosis, and the comparatively low polymorphonuclear cell count.

2. The sudden, explosive-like development of a murmur during the early stage of the illness and the very rough, high pitched quality of this murmur, in contrast to the usually insidious onset of systolic murmurs in the initial attack of acute rheumatic fever.

3. The absence of recurrent fever. It would appear from a study of the fever chart and the subsequent total absence of fever for a period of three months that we were dealing with a self-limited disease.

A remarkably constant phenomenon in an infection due to *S. suispestifer* is the low white blood cell count. Leukopenia was present in

almost every case in the series, and this is especially notable in view of the hyperpyrexia. The lowest count in the series was 4,800 and the highest 10,000. This, of course, is more or less expected to occur in bacteremia caused by any *Salmonella*, inasmuch as these organisms are members of the typhoid family.

The diagnosis of this disease is made partly by elimination of other possible infections, but is definitely established only by positive blood culture. Agglutination reactions with *suipestifer* should be borne in mind in any case of apparent typhoid or paratyphoid fever with a negative Widal reaction, but it must also be remembered that positive agglutination in high titer may not develop for many months. Moreover, a cross-agglutination between the patient's serum and paratyphoid bacillus B often occurs during the acute stage of infection caused by *suipestifer*, a fact that obscured the true identity of the latter organism until the characteristic carbohydrate fermentations were discovered and standardized. The positive blood culture and the carbohydrate reactions, therefore, lead to an accurate diagnosis; it is obvious that the matter of recognition of *S. suipestifer* requires a competent bacteriologist.

As to the endocarditis, we realize the limitations of a clinical report unsupported by pathologic evidence; the rarity of such a complication in infection with *S. suipestifer* prompted us to report its probable occurrence and in doing so to call to the attention of other observers, especially those who will be fortunate enough to see a larger number of cases, the possibility of cardiac involvement.

SUMMARY

1. A case of *S. suipestifer* bacteremia and accompanying endocarditis is described. This is the first report of the development of endocarditis as a complication of this bacteremia.

2. The frequency and symptomatology are discussed, with the citation of 34 cases previously reported.

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THE METABOLIC EXERCISE TOLERANCE TEST

A SIMPLIFIED METHOD

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In another communication,¹ a method was described for measuring the excess oxygen consumption during exercise, the oxygen debt and the time required for recovery. It was found that these measurements, particularly the excess oxygen consumption during exercise, were greater than normal in patients with organic heart disease and a history of some limitation of activity, even when no congestive heart failure was present. It was concluded that this test yields a useful objective quantitation of the cardiac capacity.

The method previously described involved the use of an extension arm on the usual Roth-Benedict basal metabolism machine, and the calculation of results from multiple slopes recorded on a long paper record made by pasting three of the standard basal metabolism sheets end to end. In the present communication we are describing a simplified method which, in addition to other advantages, facilitates the calculation of results.

METHOD

The present method differs from that previously described chiefly in the manner in which the excess oxygen consumption is recorded. The arrangement of the apparatus is shown diagrammatically in figure 1.

The spirometer is filled with oxygen from tank *A* and, if desired, the oxygen consumption during rest is determined or a basal metabolism test may be performed in the usual manner. When this is completed the clockwork drum is stopped and the spirometer is refilled from tank *A*. By means of a fine needle valve (*D*) oxygen is now introduced into the spirometer from tank *B*, through the flowmeter

Aided by the Frederick K. Babson and the Max Pam Funds.

From the Metabolic and Cardiovascular Laboratories of the Department of Physiology, the Heart Station, and the Max Pam Unit, Michael Reese Hospital.

1. Katz, L. N.; Soskin, S.; Schutz, W. J.; Ackerman, W., and Plaut, J. L.: A "Metabolic Exercise Tolerance Test" for Patients with Cardiac Disease. A Feasible Method for Using the Excess Oxygen Consumption and the Recovery Time of Exercise as Criteria of the Cardiac Status, this issue, page 710.

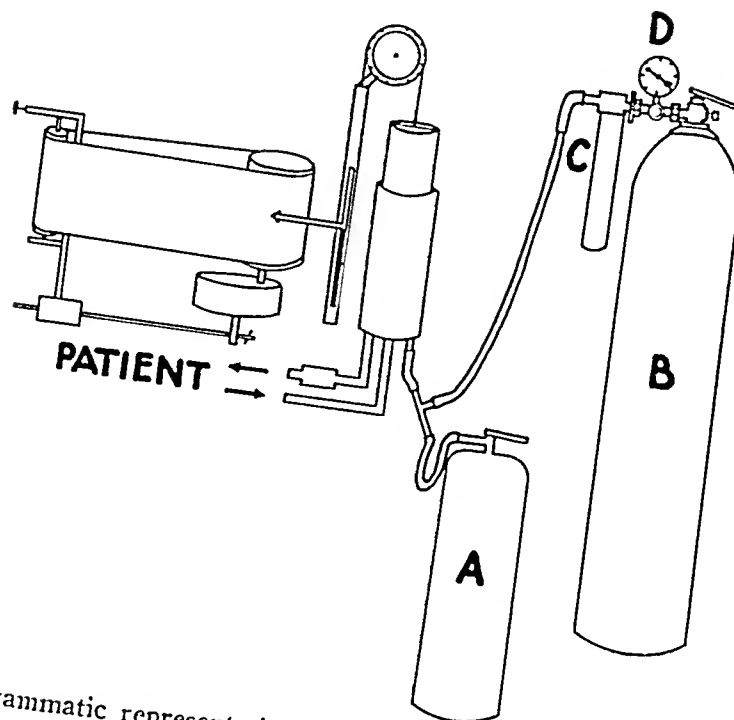


Fig. 1.—Diagrammatic representation of the apparatus for a simplified method of performing the test.

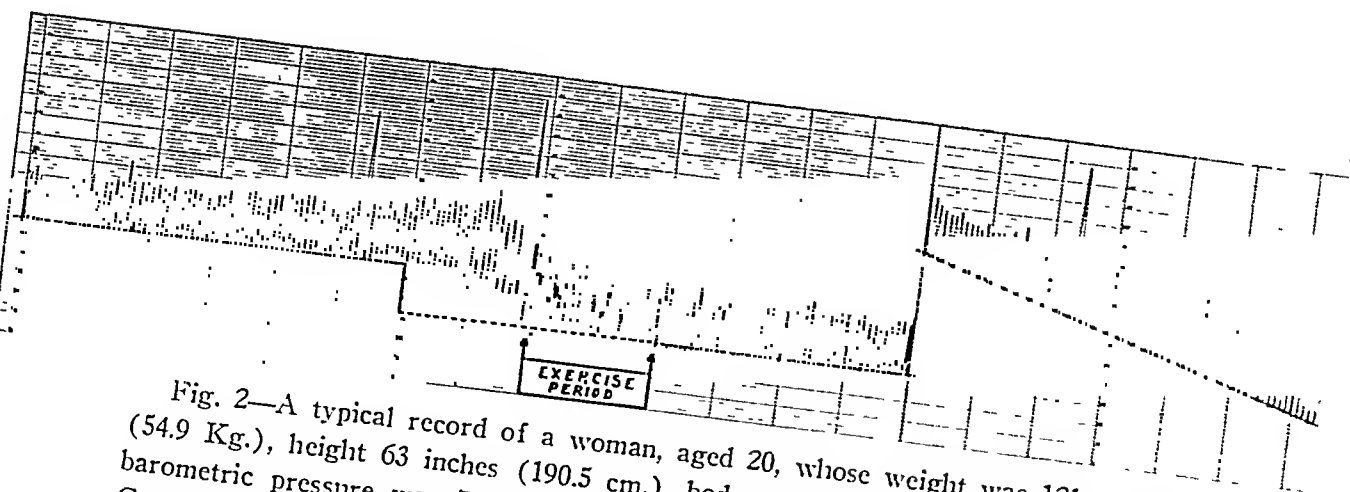


Fig. 2—A typical record of a woman, aged 20, whose weight was 121 pounds (54.9 Kg.), height 63 inches (190.5 cm.), body surface 155 square meters. The barometric pressure was 754 mm. of mercury and the average temperature 24 C. (75.2 F.). The exercise consisted in lifting two 2,625 Gm. weights through a distance of 37.5 cm. at a rate of 20 times a minute for two minutes. This represents approximately 80 kilogram-meters of work. Recovery time was two minutes. Excess oxygen consumption = $58 - 34 = 24$ mm., or $24 \times 20.73 = 497.5$ cc. of oxygen. Corrected to standard temperature and barometric pressure the result is $497.5 \times .89 = 442.8$ cc. of oxygen. The excess oxygen consumption per kilogram-meter of work per square meter of body surface = $\frac{442.8}{80 \times 1.55} = 3.6$ cc.

(C) ² at such a rate that the writing point continues to superimpose its record at the same constant expiratory level. The clockwork drum is now restarted and the record is observed for several minutes to insure the existence of an exact balance between the oxygen consumed by the resting patient and the oxygen introduced from tank *B*. Once this exact balance has been established, the adjustment of the needle valve is left unchanged for the duration of the test. Reading of the flowmeter offers an additional visual check on the constancy of the supply of oxygen at all times. With the oxygen flowing into the spirometer at a rate equal to the oxygen consumption during rest, the exercise is performed in the manner previously described, and the observations are continued until a new constant expiratory level is recorded.

The difference in height between the constant horizontal levels, before and after exercise, represents the excess oxygen consumption during the exercise. The time elapsing from the end of the exercise to the point at which the final horizontal level is first established represents the time required for recovery. The difference between the horizontal lines may be read directly from the ruled paper in millimeters and converted to cubic centimeters of oxygen by multiplying by the conversion factor 20.73.³ The volume of gas is corrected to standard temperature and pressure in the usual manner. A typical record and calculation is shown in figure 2.

COMMENT

The present simplified method gives a more compact record than the method previously described. It permits a visual check on the steady state of the patient before the exercise and his return to the resting level after the exercise. The computation of the results is simpler and less subject to error, since it eliminates the periods of time necessary for refilling the spirometer and the necessity for drawing a slope for the irregular portion of the record during the period of exercise. Certain further possible simplifications of this method are suggested in the appendix.

The simplified method for the metabolic exercise tolerance test renders it hardly more difficult to perform than the ordinary basal metabolism test, once the equipment is assembled. In this form it is suitable for routine use in the clinical laboratory. The objective nature of the test, which eliminates the subjective influence of both patient and physician, makes it particularly suitable for the accumulation of data by different observers on large groups of persons. Such an application might be made in the classification of cardiac disability for insurance purposes.

2. The flowmeter we have used is an oxygen metric flowmeter bottle, calibrated to a maximum of 650 cc., which may be obtained from the Foregger Company, Inc., New York.

3. The spirometer bell of the Roth-Benedict apparatus has a standard capacity of 20.73 cc. per millimeter of height.

SUMMARY

A simplified method is described for determining the excess oxygen consumption during exercise and time required for recovery by the metabolic exercise tolerance test.

APPENDIX

1. By using a base-line and time marker and a millimeter rule, it is possible to substitute plain kymograph paper for the ruled sheets for recording basal metabolism, thus avoiding the labor of pasting the latter together.

2. A slow moving drum may be used in conjunction with the modification just suggested to make the record more compact. This may obviate the necessity for building a kymograph extension.

3. If it is not desired to record the time required for recovery, it is possible to perform this test with the ordinary basal metabolism machine and paper. The preexercise and postexercise levels are recorded for a few minutes each, the clockwork drum being stopped during exercise and until the final horizontal seems to be established.

A "METABOLIC EXERCISE TOLERANCE TEST" FOR PATIENTS WITH CARDIAC DISEASE

A FEASIBLE METHOD FOR USING THE EXCESS OXYGEN CONSUMPTION AND THE RECOVERY TIME OF EXERCISE AS CRITERIA OF THE CARDIAC STATUS

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In accordance with the present trend of clinical medicine, there have been many attempts to devise methods for obtaining objective evidence concerning the functional condition of the heart in patients with cardiovascular disease. Such methods may be divided into two categories: (1) those which attempt to estimate the functional state of the heart at any given time, i. e., its ability to meet the routine demands of life, and (2) those designed to measure the cardiac reserve, i. e., the ability of the heart to meet emergency demands.

Most of the phenomena which have been observed under those methods have been the coincidental changes in the cardiovascular and respiratory systems, such as deviations from the normal in vital capacity, minute volume of respiration, venous pressure, minute volume of blood flow, circulation time, blood pressure and pulse rate. While these measurements within their limits of accuracy are of undoubted value in supplementing the impression gained from the history and physical examination in arriving at an estimate of the functional state of the heart, they are not necessarily related to the cardiac reserve. This objection has led to the development of various tests, which depend on the observation of the response of patients with heart disease to given

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stresses, such as muscular exercise,¹ anoxemia² and respiratory strain.³ Despite the multiplicity of tests and modifications which have been proposed, not one has proved to be of sufficient practical value to gain general acceptance and use. A number of investigators have reported that the results of such tests in normal persons and in patients with heart disease do not parallel the obvious cardiac capacity as determined by the clinical examination.⁴

The problem is complicated by the fact that any test in which the patient is required to do work is influenced not only by the functional capacity of the heart but also by the condition of the patient as a whole. The factors of nervous tension, neuromuscular coordination and training, the condition of the respiratory system and similar conditions may far outweigh the factor of the capacity of the heart in the balance struck by the test. From a practical standpoint this situation is rather to be desired, since it is the ability of the patient and not merely of the heart to do work which is important from the clinical point of view. Nevertheless, these extracardiac factors are of extreme importance in determining the value of the criteria which one uses for estimating the cardiac reserve. It is not improbable that the failure of the various tests to justify their use rests on the inadequacy of the criteria which

1. (a) Bansi, H. W., and Groscurth, G.: *Ztschr. f. Kreislaufforsch.* **22**:657, 1930; (b) *Klin. Wchnschr.* **57**:1276, 1931; (c) *Ztschr. f. d. ges. exper. Med.* **77**:631, 1931. (d) Harris, I., and Lipkin, I. J.: *Edinburgh M. J.* **38**:501, 1931. (e) Burger, M.; Burger, H., and Petersen, P. F.: *Arbeitsphysiol.* **1**:614, 1929. (f) Schneider, E. C.: Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, *J. A. M. A.* **74**:1507 (May 29) 1920. (g) Hyman, A. S.: *New England J. Med.* **202**:807, 1930. (h) Williamson, C. S.: *Am. J. M. Sc.* **149**:492, 1915. (i) Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure, *Arch. Int. Med.* **48**:377 (Sept.) 1931. (j) Cotton, T. F.; Rapport, D. L., and Lewis, T.: *Heart* **6**:269, 1915. (k) Master, A. M., and Oppenheimer, E. T.: *Am. J. M. Sc.* **177**:223, 1929.

2. Stengel, A.; Wolferth, C. C., and Jonas, L.: *Am. J. M. Sc.* **161**:781, 1921.

3. Frost, H. M.: *Boston M. & S. J.* **191**:853, 1924. MacKenzie, L. F.; Wells, P. V.; Dewis, E. G., and Ylvisaker, L. S.: *Am. J. M. Sc.* **180**:372, 1930. Eustis, A.: *Ann. Int. Med.* **5**:842, 1932; *New Orleans M. & S. J.* **81**:605, 1929.

4. Brittingham, H. H., and White, P. D.: *Cardiac Functional Tests*, *J. A. M. A.* **79**:1901 (Dec. 2) 1922. Spohr, E., and Lampert, H.: *München. med. Wchnschr.* **77**:430 and 491, 1930. Scott, V. T.: *The Application of Certain Physical Efficiency Tests*, *J. A. M. A.* **76**:705 (March 12) 1921. Wilson, M. G.: *Exercise Tolerance of Children with Heart Disease*, *J. A. M. A.* **76**:1629 (June 11) 1921. Propst, D. W.: *Exercise Cardiac Functional Test in 100 Cases of Heart Disease*, *J. A. M. A.* **82**:2102 (June 28) 1924. Scham, M., and Egerer-Scham, G.: *Physiology of Exercise: Investigation of Cardiovascular Tests in Normal Children and in Children with Tuberculosis and Valvular Heart Disease*, *Am. J. Dis. Child.* **26**:554 (Dec.) 1923.

have been used in judging the results of such tests, rather than on any inappropriateness of the test itself.⁵

It has recently been shown that patients with organic heart disease require a greater amount of oxygen to perform a given amount of work than do normal persons (Bansi and Groscurth,^{1a} Harris and Lipkin,^{1d} Herbst⁶ and Eppinger, Kisch and Schwarz⁷). This increase in the consumption of oxygen occurs largely during the period when the patient is recovering from the exercise, so that the oxygen debt is greater than normal and the recovery time is prolonged (Meakins and Long,⁸ Campbell and Sale,⁹ Nylin,¹⁰ Bansi and Groscurth,^{1a} Harris and Lipkin,^{1d} Harrison and Pilcher¹¹ and Eppinger, Kisch and Schwarz⁷). This increased cost of work to the patient with cardiac disease cannot be ascribed to a greater consumption of oxygen by the heart alone, but must depend to a considerable extent on the extra-cardiac factors mentioned previously. Nevertheless, the measurement obtained is absolute, and need not be reinterpreted in terms of other relationships. It is well known, on the other hand, that the reaction of the heart rate, blood pressure and the like to exercise may show wide variations even in normal persons. Since the previous work indicated a real relationship between the cardiac reserve and the consumption of oxygen by the patient for a given exercise, it seemed worth while to attempt to devise a clinical functional test of cardiac capacity on this basis.

METHOD

The apparatus used consisted of the Benedict-Roth basal metabolism machine to which an extension arm had been added. The auxiliary drum, which could be fixed at any position along the extension arm, allowed for the use of a long paper record which was made by pasting three of the standard sheets for measuring basal metabolism end to end. The apparatus for the exercises, which was of the ordinary weight-and-pulley type, was fixed to a solid upright portable stand, which could be clamped to the foot of any hospital bed. Sturdy posts were fixed on the guide bars of the weights on the exerciser, so as to define sharply the distance through which the weights could be moved. An automatic counting device registered the number of lifts during a test. The ropes of the exercise machine were so adjusted

5. In the case of the minute volume of blood flow, which may be admitted to be an adequate criterion, its use in patients with heart disease is precluded because of the gross inaccuracies of our present methods of measurement in just such cases.

6. Herbst, R.: *Deutsche Arch. f. klin. Med.* **162**:257, 1928.

7. Eppinger, H.; Kisch, F., and Schwarz, H.: *Das Versagen des Kreislaufes*, Berlin, Julius Springer, 1927.

8. Meakins, J., and Long, C. N. H.: *J. Clin. Investigation* **4**:273, 1927.

9. Campbell, J. M. H., and Sale, F. J.: *Effect of Exercise on Respiratory Exchange in Heart Disease: II*, *Arch. Int. Med.* **40**:237 (Aug.) 1927.

10. Nylin, G.: *Ztschr. f. klin. Med.* **118**:584, 1931.

11. Harrison, T. R., and Pilcher, C.: *J. Clin. Investigation* **8**:291, 1930.

that the subject lying on his bed could lift the weights through the required range by flexing his arms without moving the rest of his body.

The subject to be tested was allowed to rest for half an hour on the experimental bed before the exercise was undertaken. At the end of the rest period, the mouthpiece and the clip for the nose were adjusted to the patient, and the consumption of oxygen while at rest was determined. No attempt was made to determine values for basal metabolism, but no test was performed sooner than three hours after the previous intake of food. After a period of eight minutes during which the metabolism while at rest was determined, the tank was refilled with oxygen while the patient was still attached to the machine, and the second period was begun. When a minute or two of this second period had elapsed, a metronome was started and the patient was signaled to begin the exercise concerning which he had previously been instructed. His consumption of oxygen was thus recorded continuously before, during and after the exercise, the oxygen tank being refilled when necessary. The test was continued for from fifteen to twenty minutes after the end of the exercise, by which time the consumption of oxygen had usually returned to the resting level.

In prescribing the kind and amount of exercise which would be suitable for the test, it seemed desirable to select that amount of work which would not be tiring to partially incapacitated patients, but which would at the same time cause a sufficient change in consumption of oxygen in subjects with a normal exercise tolerance. By the method of trial and error an acceptable exercise was found which consisted in lifting a 2,625 Gm. weight,¹² with each arm, through a distance of 37.5 cm., at a rate of 20 times a minute for two minutes. With arms fully extended and in semisupination the subject grasped the rope handles with the hands and, in time with the metronome, flexed his arms acutely at the elbows while the shoulder joints were comparatively without motion. When the patient was unable to continue for the full period of two minutes, and stopped before completing the usual exercise, the test was continued; the amount of work was calculated from the number of strokes recorded by the automatic counting device on the exerciser, and the results were calculated on this basis.

The total consumption of oxygen during the test is obtained by adding the consumption indicated by each separate slope. The oxygen consumed during the intervals between slopes (during the period of from ten to thirty seconds required for filling the spirometer) is obtained by projecting the slopes to cover these periods. Because of the irregularity of the slope during the exercise, which is probably accounted for by changes in the tidal and residual air in the subject, a line is drawn between the two points of the graphic record at the beginning and at the end of the exercise, the actual contour of this portion of the record being disregarded. The actual total consumption of oxygen during the test is compared with the consumption of oxygen for the same period of time calculated at the pre-exercise rate. The difference between these two amounts is taken to be the excess oxygen consumption of exercise, and is expressed as the excess oxygen in cubic centimeters per kilogram-meter of work per square meter of body surface. The recovery time is the time in minutes from the end of the exercise to the moment when the consumption of oxygen first returns to the preexercise level. A typical record of a test is shown in chart 1 and table 1.

12. No inference of precision as regards these weights is intended. The figure given happened to be the sum of the weights loaded on the exerciser when the best results were obtained. No allowance has been made for friction, etc.

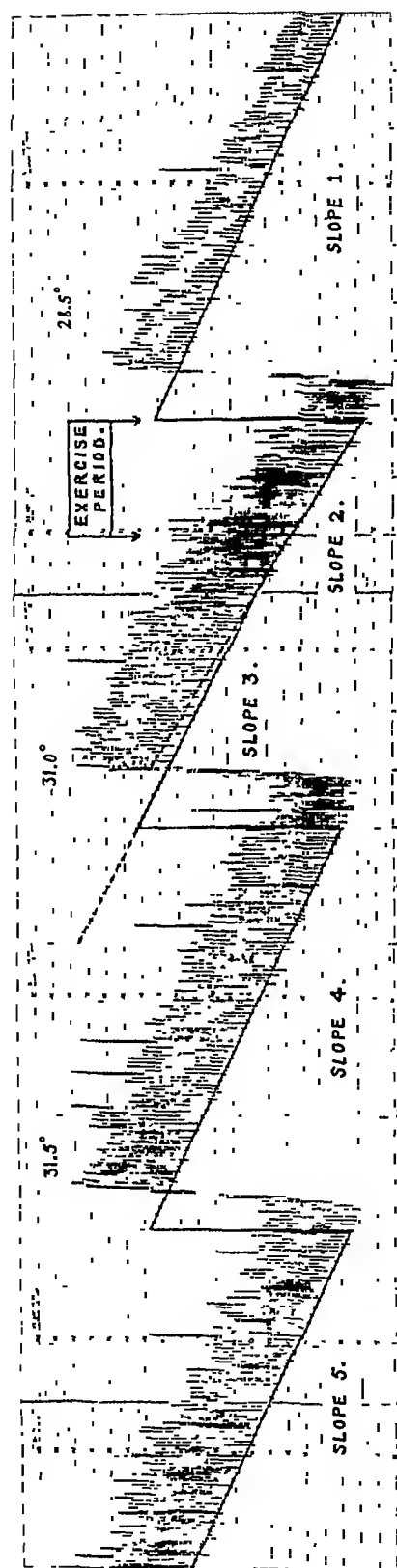


Chart 1.—Results of the test of one patient (J. B., table 3). The last food was taken four hours previous to the test.

The method of calculations is as follows:

Total actual consumption of oxygen (slopes 1 to 4) = 6,644 cc.

Consumption of oxygen for period of test (21 minutes), calculated at pre-exercise rate (slope 1) = $21 \times 296 = 6,216$ cc.

Excess consumption of oxygen of exercise = $6,644 - 6,216 = 428$ cc.

Excess oxygen per kilogram-meter of work per square meter of body surface = $\frac{428}{80 \times 1.55} = 3.5$ cc.

Recovery time (duration of slopes 2, 3 and 4 minus the exercise period of 2 minutes) = 12 minutes.

Oxygen debt = total excess oxygen — excess oxygen during 2 minute exercise period = $428 - (389 - 296) \times 2 = 242$ cc.

Oxygen debt per kilogram-meter of work per square meter of body surface = $\frac{242}{80 \times 1.55} = 2$ cc.

TABLE 1.—*Record of Test of One Patient (J. B.)*

Slope	Chart Reading for Six Minutes, Calories per Hr.	Oxygen per Minute		Actual Duration of Slope, Min.	Actual Oxygen Consumption, Cc.
		From Standard Conversion Tables, Cc.	Corrected for Temperature and Barometric Pressure, Cc.		
1.....	90	310	296	7	2,072
2.....	119	412	359	3	1,167
3.....	99	342	321	4	1,284
4.....	93	322	303	7	2,121
5.....	90	310	292	6	

The apparatus required for this test is relatively inexpensive and is such as to be readily available in most institutions. Both the basal metabolism machine and the "exerciser" are mobile and can be wheeled from bed to bed in the hospital ward, thus obviating unnecessary disturbance of sick patients who are to be tested. The selection of exercise for the arms as opposed to exercise of the muscles of the legs was made to avoid large differences in training (Herbst⁶). As in the basal metabolism test, better results are obtained after the subject has become accustomed to the procedure. Although some subjects may have difficulty in following the metronome accurately, and may therefore not perform the exact number of lifts prescribed, the actual work done is indicated by the counting device on the exercising machine, and the calculations are made accordingly.

RESULTS

Two series of subjects were tested. One series consisted of twenty-six normal persons, thirteen men and thirteen women, interns, technicians and others, apparently in perfect health, on whom a total of forty-nine tests were made. The ages of these persons ranged from 19 to 33 years. The other series of subjects consisted of fourteen men and twelve women, patients attending the Adult Cardiac Clinic of the Michael Reese Hospital, on whom a total of forty-five

tests were made. The ages of these patients ranged from 13 to 36 years, with the exception of one patient who was 45 years old.

The subjects from the clinic were selected by one of us, on the basis of age and ability to cooperate, on the day of their visit to the clinic. However, no patient showing evidence of congestive heart failure was chosen. After agreeing to submit to the test, each patient went to the Max Pam Metabolism Unit, where the tests were performed. The patients were thus not specially prepared for the test, nor were the experimenters performing the test informed of the cardiac status of the patients they were testing.

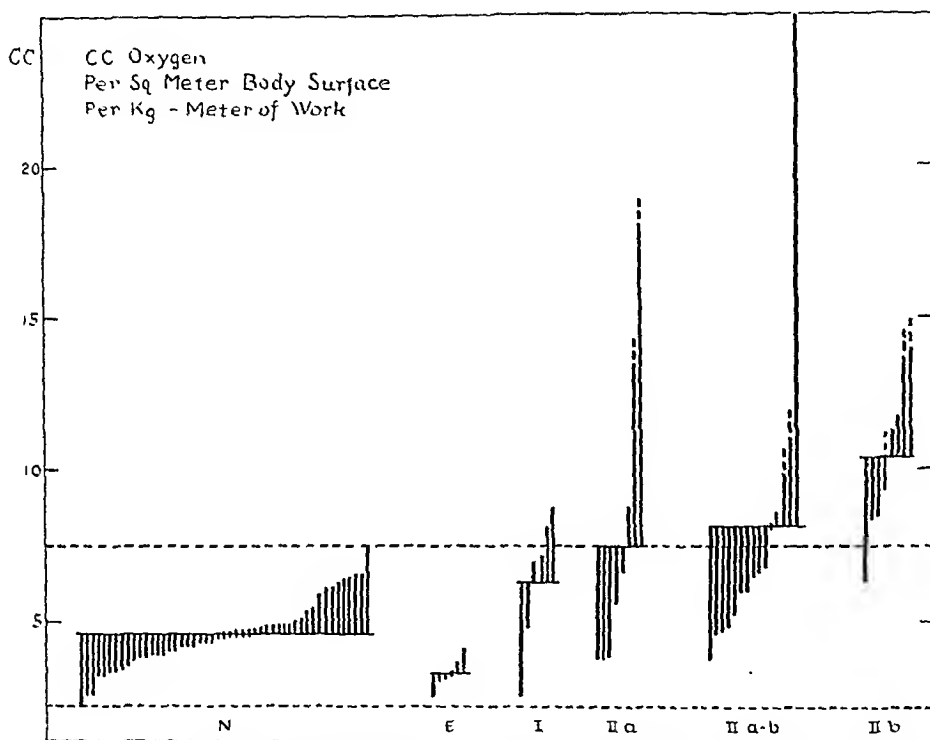


Chart 2.—The graphic comparison of the excess oxygen consumption of exercise in the normal subjects and in those with cardiac disease. In the normal group (*N*) and in each subgroup of the patients with cardiac disease (table 3, footnote *) the individual test values are drawn as vertical lines to the horizontal line, which is the mean value for the group. The horizontal broken lines represent the extreme range of the normal values. The dashes above certain of the vertical lines indicate that the tests represented by the lines were not continued to complete recovery from the exercise. The true mean value for groups containing such tests would therefore be higher than indicated.

Subsequent to the completion of this series of tests, the patients were asked to return to the clinic, at which time a clinical estimate of their cardiac status was made on the following basis: (1) history and physical examination at this time; (2) previous clinic and hospital records, and (3) information derived from social service records. The

TABLE 2.—Results of Tests of Normal Subjects

Name	Date, 1932	Age, Yrs.	Weight, Lbs.	Height, Inches	Body Sur- face, Sq.M.	Exercise			Excess Oxygen per Kg.-M. of Work per Sq.M. of Body Surface	Recovery Time, Min.	Oxygen Debt per Kg.-M. of Work per Sq.M. of Body Surface
						Strokes, per Min.	Dura- tion, Min.	Work, Kg.-M.			
J. P. (M)	1/ 2	26	185	68½	1.95	30	2	120	4.6	6	2.7
	4/12	20	2	80	5.9	12½	4.2
	4/26	20	2	80	4.3	4½	2.6
	5/14	20	2	80	6.5	3	3.5
	5/24	20	2	80	6.4	4½	3.2
W. A. (M)	1/10	25	146	66½	1.75	30	2	120	4.6	6	2.3
	3/ 6	20	2	80	5.4	8½	3.9
	4/11	20	2	80	6.1	4½	3.4
	4/23	20	2	80	3.7	3	1.9
	5/22	20	2	80	3.2	4	1.4
W. S. (M)	3/22	25	155	70	1.85	20	2	80	3.4	1½	0.4
	4/11	20	2	80	3.9	3½	2.5
	4/22	20	2	80	3.8	3½	1.4
F. R. (F)	1/15	19	100	64½	1.45	30	2	120	4.2	6	1.6
	4/ 4	20	2	80	4.0	3	1.7
L. K. (F)	2/12	22	125	63	1.55	20	2	80	6.5	4	2.8
	4/ 6	20	2	80	3.1	2	1.5
R. S. (M)	2/15	23	160	73½	1.95	20	2	80	4.0	6	1.9
	3/ 5	30	2	120	4.3	3	2.4
V. E. (F)	2/ 8	33	115	66	1.55	20	2	80	4.6	5½	2.3
	4/26	20	2	80	4.9	6	3.6
D. Z. (M)	3/ 1	22	144	66½	1.75	20	2	80	2.5	5	1.0
	3/ 8	30	2	120	2.2	5	0.8
M. M. (F)	3/22	21	150	63	1.70	20	2	80	4.9	7	2.2
	3/23	20	2	80	4.2	5	1.2
C. G. (F)	3/22	21	97	60	1.35	20	2	80	4.9	4	2.3
	4/23	20	2	80	4.5	8	3.6
E. S. (F)	4/ 6	24	106	65	1.50	20	2	80	6.1	3	1.7
	4/18	20	2	80	7.5	8	2.9
B. T. (F)	4/ 6	22	168	66	1.85	20	2	80	3.5	2½	0.4
	4/12	20	2	80	3.9	2	1.3
H. P. (M)	4/ 7	27	160	68	1.85	20	2	80	4.7	4	2.2
	4/23	20	2	80	4.8	9	3.0
R. F. (M)	4/ 7	28	150	72	1.85	20	2	80	3.3	2½	1.0
	4/18	20	2	80	4.9	3	0.7
J. R. (F)	2/18	22	123	65½	1.60	20	2	80	4.3	8	1.4
	3/ 4	20	2	80	4.6	5½	1.5
K. J. (M)	12/29†	20	162	69½	1.90	30	2	120	4.5	4	1.2
M. R. (F)	1/19	20	121	63	1.55	30	2	120	5.3	5	2.9
G. J. (M)	3/18	28	140	66½	1.70	20	2	80	6.3	5	2.8
E. O. (F)	1/15	26	126	66	1.60	20	2	80	3.9	7	2.1
A. K. (M)	2/ 8	24	142	69½	1.80	30	2	120	3.3	5	1.6
R. S. (F)	4/ 5	21	115	62	1.50	20	2	80	3.8	5	0.9
G. C. (M)	5/17	25	179	70½	2.00	20	2	80	4.9	10	1.4
I. L. (M)	4/13	21	145	68½	1.80	20	2	80	5.0	2½	0.4
A. P. (M)	4/17	24	122	69½	1.65	20	2	80	3.2	3	1.0
C. B. (F)	12/19†	23	225	66	2.10	20	1	40	4.2	3	1.1
(obese)	1/12	30	2	120	6.3	4	4.5
V. O. (F)	1/ 5	20	230	68½	2.20	30	2	120	2.5	6	0.8
(obese)											
Average.....									4.6	5	

* The work per lift = 1.97 Kg.-M. For ease of calculation the value 2 has been used instead.

† 1931.

group of physicians making these estimates were not informed of the results of the so-called "metabolic exercise tolerance tests." From this clinical survey the patients were classified in the following five divisions (modified from the classification of the American Heart Association): class E, possible heart disease, with no apparent organic lesion; class I, organic heart disease, with no history of limitation of activity; class IIa, organic heart disease, with a history of slight limitation of activity; class IIa-b, organic heart disease, with a history of moderate limitation of activity, and class IIb, organic heart disease, with a history of marked limitation of activity. The data for each series of cases are summarized in tables 2 and 3, respectively, and the results of these series are compared in charts 2 and 3.

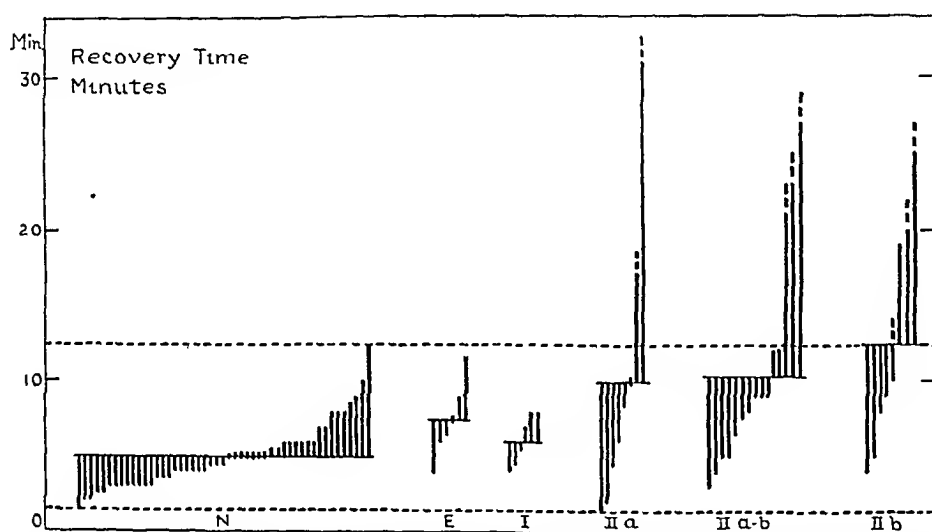


Chart 3.—The graphic comparison of the recovery time after exercise in the normal subjects and in those with cardiac disease. The conventions are similar to those in chart 2.

COMMENT

In order to arrive at comparable figures for different persons, the excess oxygen of exercise has been calculated as the excess oxygen per kilogram-meter of work per square meter of body surface. These values, for the normal persons tested, show a surprisingly normal distribution curve with a mean value of 4.6 and a range of from 2.2 to 7.5 (chart 2). The recovery time for the same group shows a similar distribution (chart 3). The ranges for both excess oxygen and recovery time are not much greater for the entire group of normal subjects than for a number of tests performed on a single normal person at intervals (J. P. and W. A., table 2).

The values for excess oxygen consumption and recovery time for class E, patients with no apparent organic heart lesions, fall well within

the normal range (charts 2 and 3). The results of these tests serve as an additional control and obviate the possibility of differences between our normal subjects and those with cardiac disease as to environment, social stratum, personal hygiene and other factors.

The excess oxygen consumption and recovery time in the groups of patients with organic heart disease show mean values which are progressively higher than the mean value of the normal subjects as one passes from the group with no limitation of activity (class I) to the group with marked limitation of activity (class IIb). There is also a progressive tendency for more of the individual values in these successive groups to be outside the normal range. It is apparent that the recovery time does not show as close a relationship to the clinical classification as does the excess oxygen consumption. However, there can be no question about the striking difference between classes I and IIb as regards both of these measurements. It is surprising that there should be such distinct graded differences in the excess oxygen consumption of classes IIa, IIa-b and IIb, considering the manner in which these groups were established. The results show that, even in the absence of congestive heart failure, patients with organic heart disease have an increased oxygen requirement and recovery time, for a given amount of work, which are roughly proportional to the history of limitation of activity.

The figures for oxygen debt in both the normal subjects and in those with cardiac disease roughly parallel the figures for excess oxygen consumption. The poorer relationship of the former to the clinical classification, however, renders it less suitable than the latter as a measure of the test. This is probably accounted for by the mild and brief nature of the exercise employed in the present series; during such a short period, the variation in different patients in the time required for adjustment to the effort may significantly affect the distribution of the excess oxygen consumption between the periods of exercise and recovery.

Our results are in agreement with those in the literature cited earlier in the article. However, a few observers claim to have found no increase in excess oxygen consumption of exercise even in patients with congestive heart failure.¹³ Such results are difficult to reconcile with our own. An examination of their protocols, however, suggests that their findings may be influenced by the fact that they did not observe their patients for a sufficiently long period following the

13. Peabody, F. W., and Sturges, C. C.: *Clinical Studies on the Respiration*, Arch. Int. Med. 29:277 (March) 1922. Alt, H. L.; Walker, G. L., and Smith, W. C.: *The Cardiac Output in Heart Disease*, Arch. Int. Med. 45:958 (June) 1930. Harrison and Pilcher.¹¹

TABLE 3.—Results of Tests of Patients with Cardiac Disease *

Name	Date, 1922	Age, Years	Weight, Pounds	Height, Inches	Body Sur- face, Sq.M.	Exercise		Excess Oxygen per Kg.-M. of Work	Recovery per Sq.M. of Body Surface Min.	Oxygen Debt per Kg.-M. of Work	Class	Heart Rhythm	Cardiac Enlarge- ment	Valve Involve- ment	Etiology	Comment
						Strokes, per M.	Dura- tion, Min.									
J. B. (M)	4/27	17	115	64	1.55	20	2	50	3.5	12	E	SR	NE	Systolic murmur at apex
S. S. (F)	3/30 4/13	16½	102	63	1.45	20	2	80	4.2	9	E	SR	NE	...	NC	
J. R. (M)	3/23	17	138	72	1.80	20	2	80	3.0	6½	E	SR	NE	Systolic murmur at apex
A. G. (M)	3/23	14	126	66	1.65	20	2	80	3.7	7½	E	SR	NE	Systolic murmur at apex
O. B. (F)	2/ 3	15½	122	62	1.55	20	2	80	2.5	4	E	ST	NE	Palpable thyroïd roughened first at apex
Average.....										7.5						
S. K. (F)	4/20	15	130	63	1.60	20	2	80	7.2	4½	I	SR	SE	Systolic over pul- monic area
B. V. (M)	4/20	18	123	66	1.60	20	2	80	7.0	7	I	SR	SE	...	CH	Systolic over base and sternum
L. D. (F)	3/ 9	25	140	67	1.70	20	2	80	2.5	4	I	SR	SE	DM	R	
S. G. (F)	2/24	20	132	61½	1.60	20	2	80	4.8	8	I	SR	SE	DM	R	
H. G. (M)	2/10 4/27	15	122	68	1.65	20	2	80	8.2	8	I	ST	SE	DM	R	Has fever on occasion
Average.....										6.4						
L. G. (F)	3/23 4/30	17	115	61	1.50	20	2	80	5.1	14	IIa	SR	ME	DM	R	
A. A. (F)	3/ 9 5/ 2	24	89	61	1.35	20	2	80	6.2	7	DA		
O. K. (M)	5/13	14½	76	58	1.20	20	1½	60	13.5+	17(NR)	IIa	SR	SE	DM	R	
W. G. (M)	4/20 4/30	18	141	67	1.70	20	2	80	8.8	8½	IIa	ST	SE	DM	R	Hyperthyroidism
										31(NR)	IIa	SR	ME	DM	R	
										2	IIa	AI		
										1½			

O. M. (M)	2/17	35	157	69½	1.85	20	2	80	6.6	10	3.9	IIa	SR	SE	DM	R	
H. K. (M)	2/10	16	131	70½	1.75	20	2	80	3.7	6	1.8	IIa	SR	ME	DM	R	
	4/30	20	2	80	3.6	4½	0.6						
Average.....									7.5+	10.0+							
H. L. (F)	1/6	16	112	63½	1.50	20	2	80	8.6	9	5.5	IIa-b	SR	ME	DM	R	
	4/13	20	2	80	11.1+	23(NR)	8.4+						
	4/30	20	2	80	6.0	12	3.1						
	5/28	20	2	80	4.7	9	1.9						
D. S. (F)	3/17	11	87½	60	1.30	20	2	80	8.2	5½	6.9	IIa-b	SR	TE	DM	R	
	4/30	20	1¾	70	9.8+	21(NR)	8.7+						
J. G. (M)	2/3	18	115	69	1.80	20	2	80	6.0	3	3.1	IIa-b	SR	ME	DM	R	Subacute bacterial endocarditis
	5/2	20	2	80	6.8	12	3.8	..	EX	...	DA	...	Quiescent
	6/27	20	2	80	5.2	8	2.4						
C. W. (M)	2/17	15	151	68	1.80	20	2	80	4.8	4	2.4	IIa b	AF	SE	DM	R	(Dead)
	5/11	20	2	80	3.7	5	1.8						
L. S. (F)	3/16	13	120	62	1.55	20	2	80	6.5	9	5.0	IIa-b	SR	SE	DM	R	
	5/14	20	2	80	6.6	5	3.0						
M. H. (F)	3/16	29	138	67	1.70	20	2	80	4.6	7½	1.6	IIa-b	SR	SE	DM	R	
	4/26	20	2	80	30.5+	27(NR)	25.3+						
Average.....									8.2+	10.5+							
B. S. (M)	2/18	16	133	60½	1.70	20	2	80	11.7	8	7.8	IIb	PT	ME	DM	R	(Dead)
	4/27	20	2	80	6.3	1	4.6	MI		
	5/18	20	2	80	8.5	5	6.7						
	5/28	20	2	80	8.1	9	6.1						
	6/25	20	2	80	11.3	19	9.6						
F. L. (M)	2/18	15	149	69	1.70	20	2	80	14.0+	20(NR)	11.3+	IIb	SR	ME	DM	R	
B. W. (F)	2/4	6	107	65	1.50	20	1¼	72	9.1+	25(NR)	6.5+	IIb	AF	TE	DM	R	(Dead)
A. M. (M)	1/1	23	125	67	1.65	20	2	80	13.7+	10(NR)	12.9+	IIb	AF	ME	DM	R	
Average.....									10.1+	12.5+							

* NR indicates that patient had not returned to previous mental state; R indicates possible heart disease, no apparent organic lesion; L, organic heart disease, no history of limitation of activity; IIa, organic heart disease, history of slight limitation of activity; IIb, organic heart disease, history of moderate limitation of activity; III, organic heart disease, history of marked limitation of activity; SR, sinus rhythm; ST, sinus tachycardia; AF, atrial fibrillation; T.E., extrasystoles; PT, paroxysmal tachycardia; SI, no cardiac enlargement; SL, slight cardiac enlargement (apex outside nipple); MI, moderate cardiac enlargement (apex up to anterior axillary line); PT, Marked cardiac enlargement (apex up to midaxillary line); DM, double mitral (stenosis and insufficiency); DA, double aortic (stenosis and insufficiency); AL, aortic insufficiency; R, rheumatic heart disease; CH, congenital heart disease; NC, neurocirculatory asthenia.

† Experiment was stopped at this time, as patient was as-spaced.

exercise. It can be seen that some of our patients without congestive heart failure did not fully recover from the exercise within twenty minutes. The rate of excess oxygen consumption at this time may be small; nevertheless, over a period of many minutes, it may significantly affect the total excess oxygen consumed.

The variation in the results of our test on the same normal subject at different times has already been pointed out. The variability is even greater in a patient with organic heart disease and a history of limitation of activity (A. A., H. L. and M. B., table 3). This is not surprising in view of the clinical history of fluctuations in well-being in such patients. This probably explains the presence of tests within the normal range in the groups of persons with cardiac disease with limitation of activity; the clinical classification is based on the history of the maximum limitations and not so much on the condition of the patient at the time of a particular examination. In view of the narrow range we have obtained in normal subjects the wider range in patients with cardiac disease does not impute the adequacy of the test we have employed; but it does indicate that we have been dealing with real variations in the individual. A series of tests on patients developing and recovering from congestive heart failure and on patients with reactivation of rheumatic infection is in progress, in order more exactly to correlate the results of our test with the condition of the patient at the time of the test.

On the basis of our results, we believe that this test holds promise of deserving a definite place in the armamentarium of the clinic for cardiac disease. Although the test shows only an approximate parallelism with the classification of the American Heart Association, the differences found may depend on: (1) the objective nature of this test as opposed to the clinical classification, which may be influenced by the subjective states of both physician and patient, and (2) the fact that the test indicates the condition of the patient at the time of observation, while the clinical classification is based on the history of recent maximum disability of the patient.

It is obvious that no test can in itself determine the prognosis and treatment of a given patient. We believe, however, that the metabolic exercise tolerance test may be a valuable adjunct in determining these important elements in the management of cardiac disease.

SUMMARY

1. A relatively simple method has been devised for measuring the excess oxygen consumption in exercise, the oxygen debt and the recovery time. This metabolic exercise tolerance test has been applied to a group

of normal persons and to a group of patients attending the clinic for cardiac disease, and the results have been compared.

2. It was found that these measurements, particularly of the excess oxygen consumption of exercise, were greater than normal in patients with organic heart disease and with a history of some limitation of activity, even when no congestive heart failure was present. When these patients are classified into subgroups, according to the history of the degree of limitation of activity, the measurements become progressively greater as one passes from the group with no limitation of activity to the group with marked limitation.

3. It is concluded that this test, which yields an objective quantitation of the cardiac capacity of a patient at the time of examination, merits further consideration as an adjunct in the study of cardiac disease.

CONGESTIVE HEART FAILURE

XIX. REFLEX STIMULATION OF RESPIRATION AS THE CAUSE OF EVENING DYSPNEA

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In the preceding paper of the present series¹ it was pointed out that the term nocturnal dyspnea includes three different clinical syndromes, which may or may not coexist in the same patient. For the first syndrome the term "evening dyspnea" was suggested. A patient suffering from this type of respiratory distress is relatively (or entirely) free from dyspnea in the morning when he awakens, but as the day passes increasing respiratory discomfort gradually develops, reaches its maximum in the evening hours and may prevent the sufferer from going to sleep. At length, either with or without the use of sedatives, he finally sleeps and in the morning awakens with less or no respiratory discomfort, only to undergo a repetition of the same cycle. It should be noted that dyspnea of this type is not paroxysmal, but that the discomfort sets in gradually.²

The present paper is concerned with an attempt to elucidate the factors concerned in the production of this syndrome. For this purpose analyses of the arterial blood, measurements of pulse rate, blood pressure, oxygen consumption, ventilation and vital capacity were made in the morning and in the evening. Except when otherwise stated, the methods used were those which have been applied in the preceding studies of the series.

From the Department of Medicine, Vanderbilt University.

1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, *Arch. Int. Med.* 53:561 (April) 1934.

2. In this description we do not refer to orthopnea. Ambulatory patients may be free from dyspnea during the day—provided they are not too active—and then on getting into bed become short of breath and have to sit up. In the majority of patients with cardiac dyspnea of any type, orthopnea is also present. The term "evening dyspnea" as used in this paper refers to respiratory distress which is worse in the latter part of the day even though the patient remains in bed in the same position throughout the day.

OBSERVATIONS ON PATIENTS WITH CONGESTIVE HEART FAILURE

1. *Comparison of Morning and Evening Values for the Blood Gases and Hydrogen Ion Concentration.*—To determine whether evening dyspnea was due to alterations in the acidity and allied functions of the blood, observations were made on three patients in the morning before breakfast and in the late afternoon or evening, all the samples of blood being drawn at least four hours after the preceding meal. Blood was obtained from the brachial artery. Analyses for oxygen and carbon dioxide were done on the Van Slyke-Neill³ blood gas apparatus, and hydrogen ion concentrations were determined by Cullen's⁴ colorimetric method. Carbon dioxide tensions were calculated from the Hasselbach formula, the value of pK' being assumed to be 6.1.

The data are shown in table 1. Eight comparisons between morning and evening values were made on the three patients, each of whom complained of more dyspnea in the latter part of the day. In six instances the oxygen capacity was slightly greater in the morning than in the evening. The opposite relationship was observed once, and no difference was noted once. The arterial oxygen saturation was, on the contrary, higher in the afternoon in seven of eight comparisons. The changes were not striking, but were well beyond the error of the methods used.

The carbon dioxide content of the arterial serum showed no constant alteration, being on an average slightly lower in the afternoon than in the morning. The values for p_H were variable. Two of the patients had more alkaline blood in the evening than in the morning, a finding which is similar to that reported by Cullen and Earle⁵ in normal persons. The third patient's blood exhibited wide but inconstant fluctuations in reaction. On an average in all observations the blood was slightly more alkaline in the evening than in the morning. The carbon dioxide tension of the blood drawn in the evening was greater twice, the same once and lower five times than the value obtained in the morning. The mean carbon dioxide pressure was slightly greater in the samples drawn in the morning.

These observations seem to indicate clearly that the tendency toward dyspnea in the latter part of the day cannot be attributed to changes in the acid-base condition of the blood. Although there was considerable variation in the individual observations, the average alterations in the

3. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61**:523, 1924.

4. Cullen, G. E.: Studies of Acidosis: XIX. The Colorimetric Determination of the Hydrogen Ion Concentration of Blood Plasma, *J. Biol. Chem.* **52**:591, 1922.

5. Cullen, G. E., and Earle, I. P.: Studies of the Acid-Base Condition of the Blood: II. Physiological Changes in Acid-Base Condition Throughout the Day, *J. Biol. Chem.* **83**:545, 1929.

blood in the evening (higher oxygen saturation, lower carbon dioxide pressure and greater alkalinity) might be regarded as effects of dyspnea, but could not conceivably have been its cause.

2. *Comparison of Morning and Evening Values of Circulatory and Respiratory Functions.*—In a further attempt to gain an insight into the mechanism of the diurnal variations in the degree of dyspnea additional observations were made. Pulse rate, blood pressure, respiratory rate, ventilation, vital capacity and oxygen consumption were measured in the morning before breakfast and at night. Blood pressures were measured with a mercury manometer. In some of the patients with aortic insufficiency the diastolic pressure could not be accurately determined and hence was not recorded. Oxygen consumption was recorded graphically with a Benedict-Roth spirometer. In some instances ventilation and respiratory rate were calculated from the tracing; in other observations the expired air was collected in a Tissot spirometer, and the respirations were counted with a stop watch. Vital capacity was determined in two patients by the usual spirometer method and in the remaining subjects by the technic described in a previous paper in the present series.⁶ The latter method is not well adapted to extremely dyspneic subjects, but is more accurate for patients who are not excessively short of breath and who breathe smoothly.

The patients were kept in bed, and no therapy was given during the day except digitalis, the dosage of which was maintained at a constant level of 0.2 Gm. daily. After the observations in the evening sedatives were administered if necessary. When the patient did not sleep, the observations made on the following day were discarded. Likewise, when a patient's clinical state necessitated any therapeutic procedure, such as the administration of morphine, diuretics or venesection, the observations made on that day were omitted from consideration. Such omissions were obviously necessary, for the study was primarily concerned with determining why the clinical state tends spontaneously to become worse later in the day, and hence any procedure which made the patient's dyspnea less in the evening than in the morning invalidated the results.

Three groups of persons were studied. Each group consisted of four men and two women. Comparisons of the measurements obtained in the morning and in the evening were made on six patients with congestive heart failure and dyspnea which was greater in the evening than in the morning. Patients with severe dyspnea were not studied.

6. Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. E., and Tins, M. M.: Studies in Congestive Heart Failure: XIV. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, *J. Clin. Investigation* **10**:833, 1931.

TABLE 2.—A Comparison of Morning and Evening Measurements of Circulatory and Respiratory Functions in Patients with Evening Dyspnea

Subject	Sex	Chief Diagnosis	Date	Cardiac Rate per Minute		Systolic Blood Pressure, Mm. of Mercury		Diastolic Blood Pressure, Mm. of Mercury		Respiratory Rate per Minute		Ventilation per Minute, Liters		Mean Tidal Air, Cc.		Oxygen Consumption per Minute, Cc.		Vital Capacity, Liters	
				A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
R. S.	M	Arteriosclerosis	12/12/31	96	87	144	156	90	86	15	21	7.16	9.62	478	458	285	287	2.61	2.20
E. G.	M	Syphilitic aortic insufficiency	12/18/31 12/19/31 12/21/31 12/23/31 1/3/32	104 ... 90 92 88	96 ... 87 94 88	214 ... 170 176 164	186 ... 180 162 174	70 ... 70 78 80	74 ... 80 90 80	18 17 20 20 18	18 19 31 15 20	12.20 ... 10.40 8.18 6.70	11.44 ... 12.00 6.43 9.12	678 ... 521 409 372	636 ... 388 428 456	288 ... 276 268 300	287 ... 304 300	2.43 2.57 2.37 3.01 2.58	2.13 2.40 2.57 2.57 2.78
M. G.	F	Hypertension	12/10/31 12/11/31 12/11/31 12/16/31 12/17/31	100 108 84 84 72	104 102 99 76 96	194 168 144 140 134	166 182 170 134 170	84 85 70 60 68	80 80 80 64 60	20 20 20 22 24	20 26 26 27 25	8.95 8.29 7.01 7.43 9.10	10.35 9.20 9.62 10.20 11.13	309 414 350 338 379	334 354 343 372 445	276 261 251 266 231	287 285 278 265 300	1.82 1.82 1.88 1.99 1.91	1.30 1.57 1.82 1.77 1.84
S. U.	F	Rheumatic aortic insufficiency	12/15/31 12/16/31	72 72	66 67	124 136	122 128	80 80	68 76	17 17	19 18	7.67 7.43	8.88 8.64	452 437—	465 480	253 256	279 277	3.44 3.28	3.11 3.21
A. O.	M	Syphilitic aortic insufficiency	1/5/31	60	47	156	160	2.78	2.69
J. D.	M	Syphilitic aortic insufficiency	10/15/31 10/16/31 10/17/31 10/18/31	2.20 2.30 2.30 2.25	2.15 2.20 2.10 2.15
E. G.	M	Syphilitic aortic insufficiency	10/15/31 10/16/31 10/17/31 10/18/31 10/19/31	2.85 2.65 2.65 2.75 3.00	2.49 2.40 2.50 2.60 2.70

as respiratory measurements may cause such patients considerable discomfort and also are rather unreliable. Four of the six patients had been studied in the past and were well accustomed to the various procedures involved.

For purposes of control, observations were made on six patients without cardiac disease and on six subjects with cardiac lesions but without dyspnea.

The data obtained from the patients with evening dyspnea are shown in table 2. Constant differences in pulse rate and in the systolic and diastolic blood pressures were not found, these functions being greater in the morning in some observations and of larger magnitude in the evening in other observations. The average values for these functions were practically identical, as shown in table 3. It is therefore evident that evening dyspnea cannot in general be ascribed to tachycardia developing during the day and likewise is not dependent on increased cardiac work because of a rising blood pressure in the evening hours.

Unlike the circulatory functions, the respiratory factors exhibited rather definite alterations during the day. In one of thirteen comparisons the rate of breathing was slower in the evening than in the morning, and in three additional instances significant alterations were not noted. In the remaining nine observations the breathing was faster in the evening by two or more breaths per minute, and in five of these the difference was marked. The average respiratory rate was 20 in the morning and 23 in the evening—an increase of 15 per cent. (The individual figures in the tables are averages of the respiratory rate for six or more minutes. Hence, differences of two or more can be regarded as significant.)

The ventilation was greater in the morning in two of twelve observations, the evening ventilation being greater in the other ten instances. (When one recalls the influence of psychic disturbances on ventilation and the difficulties inherent in making respiratory measurements on dyspneic patients it is not surprising that occasional exceptional results occur.) The average ventilation in the evening (9.66 liters) was approximately 15 per cent greater than that in the morning (8.36 liters).

Variations in the tidal air were inconstant. Some patients with rather severe evening dyspnea breathed more deeply in the morning, but in other observations the reverse change was noted, and the average values for tidal air were practically identical.

In chart 1 are shown spirometric tracings which represent marked differences in the rate of breathing at the different hours of the day. The variations usually observed were somewhat less striking than these but were usually qualitatively similar.

The consumption of oxygen was greater in the evening nine times and unchanged from the morning value twice, the average increase in the eleven observations being approximately 10 per cent.

Vital capacities were compared in twenty-three instances, and in twenty-two of these it was greater in the morning than in the evening. In six observations the difference was so small as to be within the limits of error of the methods used, but in the remaining sixteen com-

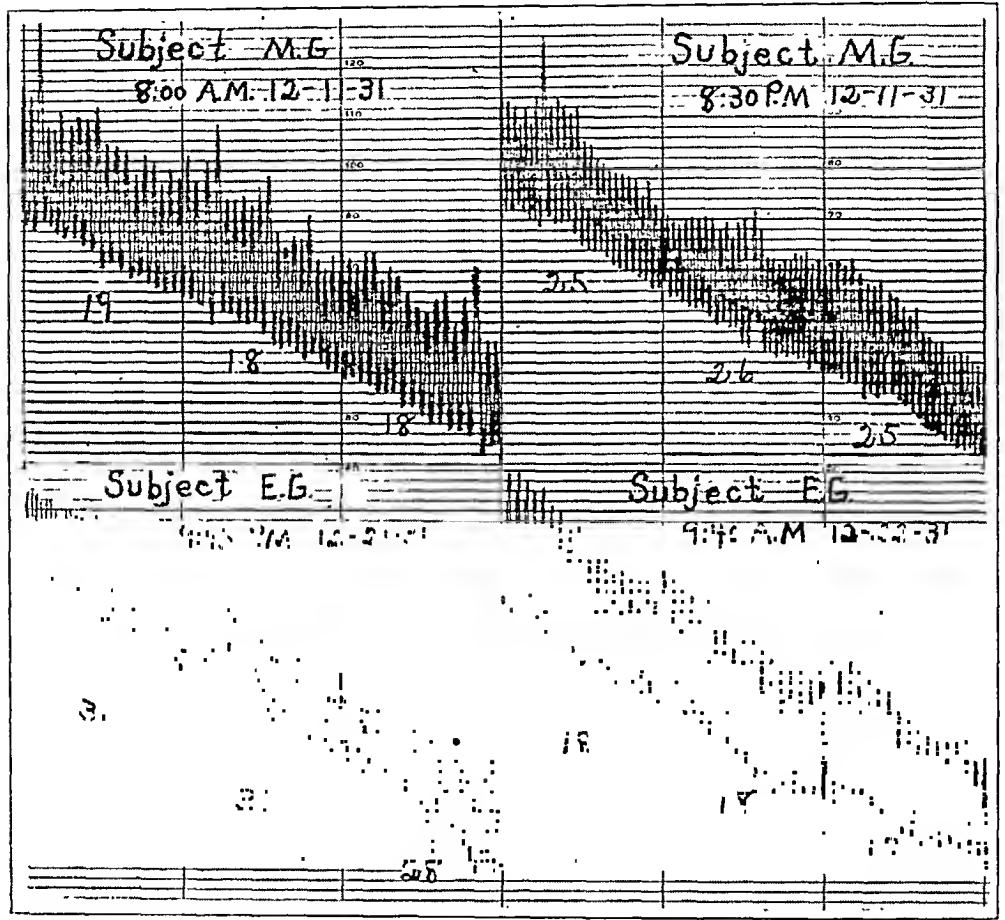


Chart 1.—The two upper curves represent observations made in the morning and afternoon, respectively, for the same patient. The two lower curves were obtained from another subject, the one on the left being taken in the afternoon and the one on the right the following morning. Both of these patients had more marked respiratory distress in the evening than in the morning and exhibited well marked increase in respiratory rate and in ventilation. In less dyspneic patients the differences were usually not as marked as these.

parisons the difference was 100 cc. or more. The average change in vital capacity in the evening was a decrease of 180 cc. or approximately 8 per cent as compared with the value in the morning. This slight but consistent decrease in the vital capacity in the evening did not occur on the days on which special therapeutic procedures were instituted.

Such measures often caused a reversal of the usual findings, the vital capacity being greater later than early in the day. The curves in chart 2 illustrate this fact. Following diuretics, phlebotomy or the administration of morphine the patients experienced a lessening of the dyspnea and coincidentally there was some rise in the vital capacity. As our study deals only with the mechanism of the dyspnea which is worse in the evening, all observations made on days when such therapeutic measures were instituted have been discarded from consideration.

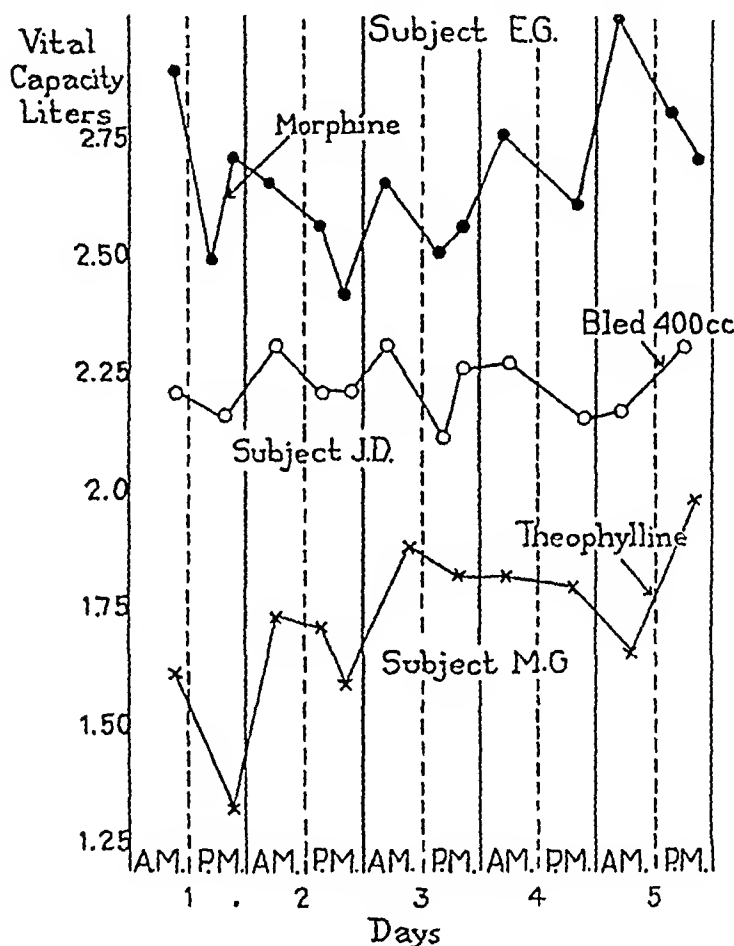


Chart 2.—These curves are illustrative of the usual slight reduction of vital capacity in the evening as compared to the morning in patients who were kept in bed but given no treatment. Any therapeutic measure administered during the day was likely to be attended by a reversal of the usual relationship.

As has been mentioned, control studies were made on subjects without cardiac disease and on persons with cardiac lesions but without evening dyspnea. For the sake of brevity the complete data for these two groups of subjects are omitted, but in table 3 the average values obtained for these groups are compared with those of the dyspneic patients.

As regards the circulatory functions, it can be seen that neither group of patients with cardiac disease exhibited variations in cardiac

rate, whereas the subjects without cardiac disease had slightly faster rates in the evening than in the morning. Significant diurnal changes in systolic blood pressures were not observed in any of the groups, although the average systolic pressure was highest in the dyspneic patients and lowest in persons in the group without cardiac disease. The diastolic blood pressure was about 10 per cent lower in the evening than in the morning in both of the control groups. It seems probable that this finding is to be interpreted as evidence of some vascular relaxation during the course of the day. The dyspneic patients failed to show this decrease in diastolic blood pressure in the evening. However, it seems extremely unlikely that this fact can account for the dyspnea, as the average diastolic pressure when they were dyspneic was exactly the same as the average value observed in the morning when they were free from dyspnea. Although we have no evidence concerning the exact cause of the absence of the decline in diastolic pressure in the evening, it seems likely that there may be some relation between this factor and the as yet unexplained tendency for the blood pressure to be elevated in persons with congestive heart failure (*Stauungshochdruck*).

The consumption of oxygen behaved similarly in all groups, the average value being approximately 10 per cent higher in the evening than in the morning. The average consumption of oxygen of the patients with congestive cardiac failure was only about 5 per cent higher than that of the other groups. This fact is noteworthy in view of the rather numerous reports in the literature of elevated metabolic rate in persons with cardiac disease.

Despite the greater consumption of oxygen, the respiratory rate and ventilation of the subjects with normal hearts were not significantly increased in the evening. The persons with cardiac disorders but without evening dyspnea had no increase in respiratory rate, but did have, on the average, a slight increase in ventilation in the evening. However, patients with evening dyspnea had a definite increase in both of these functions during the day, the average evening values being about 15 per cent above the morning level.

In all three groups the average values for the vital capacity were lower in the evening than in the morning, but in the nondyspneic subjects the difference was extremely small and less than the error of measurement. In the dyspneic patients the average difference was considerably greater, occurred in almost every instance (table 2) and was beyond the error of measurement.

When the various groups are compared with each other as regards respiratory measurements it is seen that the respiratory rates and ventilation were least in the subjects without cardiac disease and greatest in the dyspneic patients. As would be expected, the reverse relationship

was found in regard to the vital capacity. In each of these functions the patients with cardiac disease but without dyspnea showed an intermediate value.

For the purpose of expressing the degree of dyspnea in a more nearly quantitative form calculations were made of the quotient: $\frac{\text{ventilation per minute}}{\text{vital capacity}}$. It was shown in a previous study that this ratio is a fairly accurate numerical guide to the intensity of dyspnea produced by exertion; and the same relationship holds good for dyspnea at rest, provided there is no obstruction to the breathing. The values for this

TABLE 3.—Average Values for Morning and Evening Circulatory and Respiratory Measurements

	Subjects Without Cardiac Disease			Subjects with Cardiac Disease but No Dyspnea			Subjects with Cardiac Disease and Evening Dyspnea		
	Morn- ing	Even- ing	Change from Morning Value, per Cent	Morn- ing	Even- ing	Change from Morning Value, per Cent	Morn- ing	Even- ing	Change from Morning Value, per Cent
Cardiac rate per minute....	81	87	+ 7.4	73	73	0	86	86	0
Systolic blood pressure, mm. of mercury.....	126	123	— 2.4	140	137	—2.1	159	161	+ 1.3
Diastolic blood pressure, mm. of mercury.....	81	72	—11.1	75	68	—9.3	76	76	0
Respiratory rate per min.	13	14	+ 7.7	17	17	0	20	23	+15
Ventilation per minute, liters.....	6.65	6.70	+ 0.8	7.56	8.25	+9.1	8.36	9.66	+15.6
Oxygen consumption per minute, cc.....	248	276	+11.3	251	269	+7.6	261	286	+ 9.6
Vital capacity, liters.....	3.96	3.88	— 2.0	2.92	2.89	—1.0	2.51	2.32	— 7.6
Ratio of ventilation to vital capacity.....	1.68	1.73	+ 3.0	2.60	2.85	+9.6	3.33	4.16	+24.9

quotient were highest in the dyspneic patients and lowest in the subjects without cardiac disease, as shown in table 3. In the latter subjects there was little difference between the figures for morning and for evening, but the patients with dyspnea exhibited a marked rise in this quotient, which was about 25 per cent higher in the evening than in the morning. This does not mean, however, that their dyspnea was greater only by one fourth in the evening than in the morning. There is a threshold value above which this quotient must rise before a patient feels dyspneic at all. Once this quotient (which we have called the "resting ventilation index" in order to distinguish it from the value obtained with exercise, which has been called the "ventilation index") passes above the threshold of dyspnea any further rise is associated with a relatively great increase in the degree of dyspnea.

An analogy will serve to make the last sentence somewhat clearer. Let us suppose that a person has a renal threshold for sugar of exactly 180 mg. per hundred cubic centimeters of blood. Now if the blood sugar rises from 100 to 170 mg. he will have no glycosuria. At 180 mg. there will be just the slightest trace of sugar in the urine. But from that point on even a very slight further increase in blood sugar will result in a relatively marked increase in the degree of glycosuria. A rise of 10 per cent in the blood sugar (to 200 mg.) will be attended by an increase of much more than 10 per cent in the amount of sugar in the urine.

By numerous observations on many patients in the course of the past two years we have established the fact that (under the conditions in which our observations have been carried out, i. e., using valves of a given resistance) the threshold for dyspnea at rest lies in the general region of values of from 3 to 4 for the resting ventilation index. The threshold is higher in phlegmatic persons and lower in excitable ones (as is the threshold to pain), but in all those who are not either obviously hypersensitive or in a state of depressed sensibility because of drugs or disease the threshold is in the region mentioned.

Now, as can be seen from table 3, the persons in the first two groups have values for the resting ventilation index which are below this threshold region. The patients with congestive failure had, however, resting ventilation indexes which were on an average just at this level in the morning, and which exceeded it in the evening as dyspnea set in.

The data which have been presented seem to indicate that the explanation for evening dyspnea is not to be found in changes in the composition of the blood but is related to diurnal changes in the vital capacity and in the ventilation, the alterations in both of these functions being in the direction of increased dyspnea. We do not intend to imply that a person is more short of breath because he has a greater ventilation, but mean that both the subjective sensation of respiratory distress and the increase in ventilation are parallel responses to the same stimulus. The increase in ventilation, being objective, can—when considered in relation to the vital capacity—be used as a measure of the distress. Thus the problem of the cause of evening dyspnea involves at least two questions: 1. Why is the ventilation greater in the evening? 2. Why is the vital capacity lower in the evening?

At first thought one might suppose that the increase in metabolic rate in the evening was the direct and immediate cause of the greater ventilation. However, the data do not support such a conclusion, because:

1. The ventilation of the patients with congestive heart failure increased in greater degree than did their metabolic rates.

2. The control subjects exhibited as great an increase in consumption of oxygen in the evening as did the dyspneic patients, but the former subjects had either no change or a much smaller increase in ventilation.

Another possibility suggested itself as to the cause of the increase in ventilation. It was shown in a previous study⁷ that certain procedures leading to a decrease in the vital capacity of dogs caused reflex acceleration of breathing and augmentation of ventilation, the afferent path from the lungs being through the vagus nerves. Hence, one might conclude that the greater ventilation associated with evening dyspnea was due to reflex respiratory stimulation associated with events causing the decline in vital capacity which took place during the day. However, such a conclusion did not seem to us justifiable without further experimental confirmation because the daily decline in vital capacity in our patients was often very slight and sometimes less or barely more than the experimental error, whereas, in the study previously referred to only the effects of relatively great diminutions in vital capacity were investigated. Therefore the question arises: Can an increase in pulmonary congestion of such slight degree as to produce a barely measurable decline in vital capacity cause reflex stimulation of breathing? In order to answer this question it was necessary to resort to animal experimentation.

EXPERIMENTS ON DOGS

The animals were anesthetized with barbital and prepared according to the technic described in a previous study.⁷ The chest was opened, a cannula was inserted in the left primary branch of the pulmonary artery, and the left pulmonary veins were tied. The wound was then sutured in such a way as to make an air-tight closure around a small piece of rubber tubing which was connected to the cannula. By this method it was possible to produce at will "congestion" of the left lung, since blood introduced into the artery could not escape from the lung.

Following the operative procedure artificial respiration was discontinued, and the animal was allowed a few minutes in which to establish spontaneous breathing at a constant level. Observations were then made concerning the effect of introducing small amounts of blood into the left lung. In order to determine whether the effects of congestion on the respiration were of the same order of magnitude as those produced by other procedures causing a similar decrease in the volume of the lung, observations were also made on the effect of introducing similar amounts of air into the pleural cavity. It has been previously shown that either of these procedures leads to a well marked reflex stimulation of respiration.

Typical results are shown in charts 3 and 4. The introduction of 25 cc. of air into the pleural cavity was usually attended by an immediate but slight and temporary increase in the respiratory rate. Different animals reacted differently, but in none of them was there a sustained increase in the rate of breathing of more than 2 respirations per minute. When 25 cc. of blood was introduced into the pul-

7. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure: XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing, *J. Clin. Investigation* **11**:133, 1932.

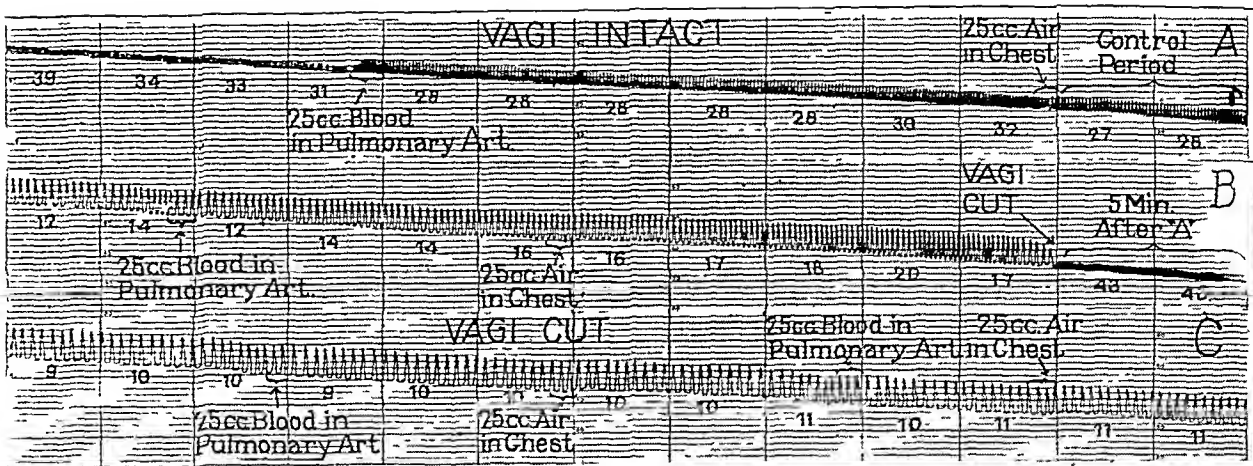


Chart 3.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers beneath the curves indicate the respiratory rate per minute. Curve *A* represents conditions with the vagus nerves intact. Injection of 25 cc. of air into the right pleural cavity caused a temporary stimulation of respiration, whereas progressive and sustained effects followed injection of a similar amount of blood into the vascular bed of the left lung, from which it could not escape because the veins were ligated (see text). Cutting the vagus nerves slowed the respiratory rate (*B*) and the same procedures which had previously caused stimulation of respiration were without effect.

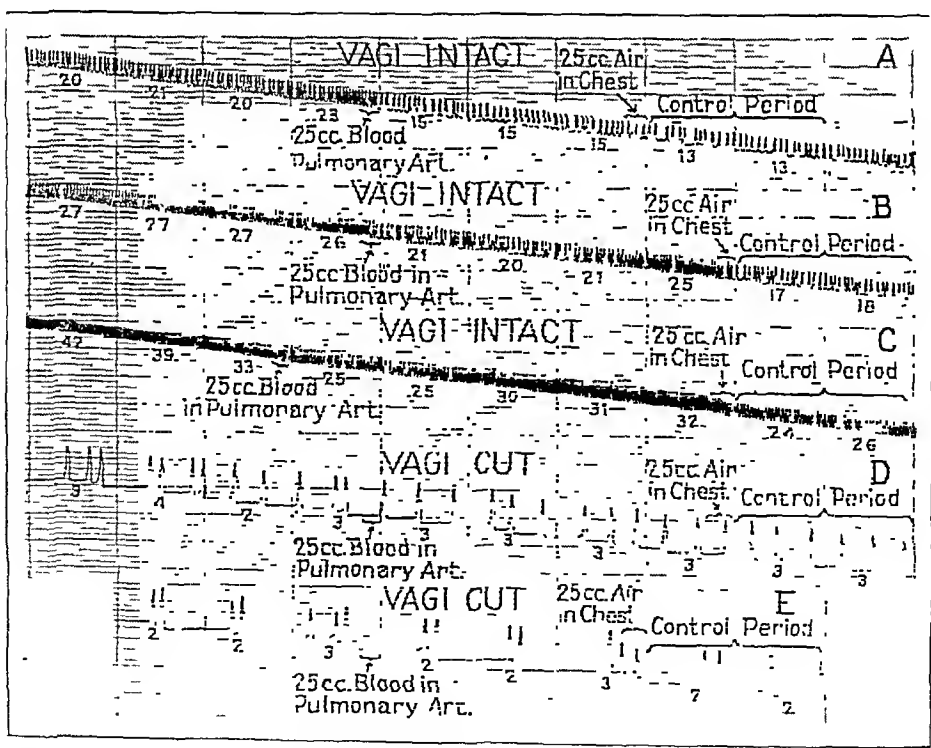


Chart 4.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers beneath the curves indicate the respiratory rate. Injection of blood into the vascular bed of the left lung caused in each instance a more sustained stimulation of respiration than did injection of air into the right pleural cavity (*A*, *B*, *C*). After vagotomy the same procedures were without significant effect (*D*, *E*).

monary vascular bed, the increase in respiratory rate and in ventilation was usually more pronounced, the effect was always longer sustained, and in several experiments the increase in breathing was progressive over a period of several minutes. In vagotomized animals significant effects on respiration were never produced by either of the procedures in question.

These experiments show clearly that pulmonary congestion causes reflex stimulation of respiratory rate and increase in ventilation, provided the increase in respiratory rate is not too extreme—in which cases the very shallow breathing may be associated with diminished minute ventilation. They also indicate that congestion is relatively more effective than pneumothorax in stimulating breathing.

It is not likely that an anesthetized dog is more sensitive to reflex respiratory stimulation than a conscious man. Therefore, since the degree of congestion produced by 25 cc. of blood in a dog's lung is sufficient to cause marked increase in breathing, it seems justifiable to conclude that the degree of congestion which can produce a decrease of from 100 to 300 cc. in the vital capacity of man (in the evening as compared to the morning) could have been responsible for the increase in respiratory rate and ventilation which our patients exhibited in the evening.

COMMENT

There is ample clinical and experimental evidence to indicate that the chief cause of the decreased vital capacity in persons with cardiac failure is congestion of the lungs. The diminution and increase of vital capacity as congestive failure develops and disappears, when taken in conjunction with the fact that the lungs of patients dying of cardiac failure almost invariably show evidence of chronic engorgement, constitute convincing although indirect evidence that congestion is the chief cause of the decrease in vital capacity in such patients. Direct experimental confirmation of this conclusion is afforded by the experiments of Drinker, Peabody and Blumgart,⁸ who found that compression of the pulmonary veins of the cat resulted in decrease in the pulmonary air space in these animals.

The data which have been presented seem to indicate that evening dyspnea is to be attributed to an increase in the degree of preexisting pulmonary congestion, which has two effects: In the first place it lowers the vital capacity and thereby tends to cause greater respiratory distress for any given level of ventilation. In the second place the greater pulmonary congestion, even if so slight as to cause a barely measurable decline in vital capacity, causes reflex stimulation of respiration with a resulting increase in the rate of breathing and in the minute ventilation. The sum total of these effects is to produce a rise in the quotient, $\frac{\text{ventilation}}{\text{vital capacity}}$, which is a measure of the degree of dyspnea. The average increase in this quotient in the evening as compared to the morning

8. Drinker, C. K.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, *J. Exper. Med.* **35**:77, 1922.

was 25 per cent. Such a change would be negligible in a person with normal lungs, but in a patient whose respiratory reserve is already lowered in the morning this change may be sufficient to produce considerable subjective respiratory discomfort in the evening.

Why are patients' lungs usually more congested (as revealed by the decrease in vital capacity) in the evening than in the morning? The answer to this question seems fairly obvious. In the morning the body functions are at a low ebb. Even though the patient remains in bed, there is a slight increase—which was, on the average, about 10 per cent in our cases—in metabolic rate during the day. It is well known that an increase in the activity of organs tends to be associated with an increase in their supply of blood. Hence, the venous return to the heart must be somewhat greater during the latter part of the day than in the morning, and the output of the right ventricle will tend to increase. If the left ventricle has less reserve power than the right ventricle (i. e., if the degree of dilatation of the left ventricle is relatively greater than that of the right) it will be less able to expel the incoming blood, and congestion of the lungs will necessarily result. In order for this to occur there need be no measurable decrease in the output of the left ventricle. A difference of 10 cc. per hour would account for the decrease in vital capacity which our patients showed. If the heart rate is 80 per minute the right ventricle only needs to pump about one thirtieth of a drop more blood at each beat than the left in order for enough additional congestion to occur in a period of twelve hours to account for the phenomena observed.

It should be pointed out that the sequence of events mentioned is not in accord with the "diminished cardiac output" theory of dyspnea. It is the increase in output of the right ventricle (owing to the greater activity of the body in the waking as compared to the sleeping state) which initiates the events leading to dyspnea. Although one has to postulate a relative diminution in the output of the left ventricle as compared to the right, the change is so slight—i. e., a difference of perhaps 100 or 200 cc. out of a total cardiac output of at least 2,000 liters in twelve hours—as to be entirely without significance when viewed as a decrease in the blood supply to the tissues. It has been customary to think of cardiac dyspnea of all types as being of chemical origin and as due to an insufficient supply of blood to the respiratory center. Our observations on evening dyspnea indicate that, like orthopnea and the dyspnea of mild exertion, it is of reflex origin, is due to "back pressure," and that it need not be associated with any measurable change in the minute cardiac output.

SUMMARY

A comparison has been made between morning and evening values of the gases in arterial blood and of respiratory and circulatory functions in a group of patients who had congestive heart failure and who suffered from dyspnea which was more marked in the evening than in the morning. The following results were obtained: 1. The oxygen capacity of the blood tended to be higher in the morning, and the oxygen saturation was usually greater in the evening. The differences were usually so slight as to be negligible.

2. Consistent variations were not observed in the hydrogen ion concentration, the carbon dioxide content or the carbon dioxide pressure of the blood. On an average the blood was slightly more alkaline in the evening and had slightly lower values for carbon dioxide content and carbon dioxide pressure.

3. No consistent alterations in heart rate or blood pressure were observed.

4. The consumption of oxygen was about 10 per cent higher in the evening than in the morning. The respiratory rate and minute ventilation were greater in the evening by an average of 15 per cent. The vital capacity was slightly lower in the evening in practically every instance, but the difference found was often not greater than the error of measurement.

5. Control observations were made on a group of patients without cardiac disease and on a group of patients with cardiac disease but without dyspnea. These two groups differed from the dyspneic subjects in the following results: (a) Their diastolic blood pressures were usually lower in the evening than in the morning, whereas no change was observed in the patients with dyspnea.

(b) Although their increase in consumption of oxygen in the evening was of about the same degree, they exhibited no increase in respiratory rate and much smaller increases in ventilation. Likewise, the control group did not exhibit constant changes in vital capacity.

Experiments were performed on dogs in order to determine whether pulmonary congestion of such slight magnitude as to cause a barely measurable decrease in vital capacity could cause reflex stimulation of respiration. The following results were obtained: 1. In animals with intact vagus nerves the introduction of as little as 25 cc. of blood into the left pulmonary artery (the left pulmonary veins being tied) led to a well marked increase in respiratory rate and in ventilation.

2. Introduction of the same amount of air into the right pleural cavities of the same animals caused less marked and less sustained respiratory stimulation.

3. After bilateral vagotomy the introduction of blood or air produced no significant changes in respiration.

As a result of these clinical and experimental observations the following conclusions are drawn:

1. The pulmonary afferent fibers of the vagus nerve are extremely sensitive to pulmonary congestion. A very small amount of excess blood in the pulmonary vascular bed causes a well marked reflex stimulation of breathing.

2. Evening dyspnea in patients with congestive heart failure is probably to be attributed to reflex respiratory stimulation and a decrease in vital capacity because of an increase in the degree of the preexisting pulmonary congestion. The greater congestion of the lungs in the evening than in the morning is believed to be due to greater bodily activity during the waking hours.

NATURE AND SIGNIFICANCE OF HEART SOUNDS AND OF APEX IMPULSES IN BUNDLE BRANCH BLOCK

J. K. LEWIS, M.D.

SAN FRANCISCO

King¹ and King and McEachern² described a group of physical signs by means of which they were able to recognize bundle branch block in 85 per cent of patients with this condition. These signs consist of a visible or palpable double apical impulse, reduplication of the first sound at the apex, an asynchronous first sound and murmur and asynchronous systolic murmurs. The abnormal impulse was found in over 80 per cent of their patients and was regarded as the most important sign. A reduplicated first sound was present in 56 per cent of their patients, and the other signs mentioned occurred less frequently. In a number of patients they obtained graphic evidence of the presence of a double systolic apical impulse by photographing the movements of a straw or its shadow attached to the chest wall at the site where the abnormal impulse was seen or felt.

No other systematic study of the physical signs in bundle branch block has been made, but it is evident from reports dealing with other aspects of this condition³ that abnormal physical signs of various kinds have been observed. Canter or gallop rhythm and reduplicated first sounds have been described, and occasionally reference has been made to the occurrence of an abnormal impulse. The type of electrocardiograms which White⁴ found associated with gallop rhythm also points to the fact that abnormal physical signs are common in bundle branch block. Intraventricular block was present in 38 per cent of the sixty-four electrocardiograms which he obtained in a group of one hundred patients with gallop rhythm, and was the most frequent electrocardiographic characteristic observed. As intraventricular block is not a

From the Department of Medicine, Stanford University School of Medicine.

1. King, J. T.: The Clinical Recognition and Physical Signs of Bundle-Branch Block, *Am. Heart J.* **3**:505, 1928.

2. King, J. T., and McEachern, D.: The Nature of the Physical Signs of Bundle-Branch Block, *Am. J. M. Sc.* **183**:445, 1932.

3. (a) Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, *Arch. Int. Med.* **13**:803 (May) 1914. (b) Cowan, J. R., and Bramwell, J. C.: The Clinical Aspects of Bundle Branch Block, *Quart. J. Med.* **19**:95, 1925. (c) Bach, F.: On the Clinical Significance of Right Bundle-Branch Block, *ibid.* **23**:261, 1930.

4. White, P. D.: The Clinical Significance of Gallop Rhythm, *Arch. Int. Med.* **41**:1 (Jan.) 1928.

frequent abnormality, his findings indicated that gallop rhythm is a common physical sign in this condition. Protodiastolic gallop rhythm was the most frequent type; systolic gallop rhythm was present in one patient. While the foregoing observations indicate that abnormal physical signs of one kind or another are not uncommon in patients with bundle branch block, none of them suggests that these signs are useful in the diagnosis of this condition.

Since King's¹ first paper appeared, Hill,⁵ Christian⁶ and Graybiel and Sprague⁷ have commented on the possibility of making the diagnosis of bundle branch block by the use of these signs. Hill and Graybiel and Sprague did not feel that the diagnosis could be made on clinical grounds, but Christian stated that one could make the diagnosis at the bedside with the aid of these signs.

A few observations on the character of the physical signs in bundle branch block have been made by means of records of the heart sounds and apex cardiograms. T. Lewis⁸ recorded abnormal sounds which he called reduplicated first sounds⁹ in four patients. In these patients the abnormality was due to an extra sound occurring late in diastole. It followed the P wave by a longer interval than the extra sound in the average patient with gallop rhythm, and its appearance was often similar to that of the first heart sound. In another paper, T. Lewis¹⁰ referred to this abnormality as canter rhythm. Battaerd¹¹ recorded the sounds

5. Hill, I. G. W.: Bundle-Branch Block: Clinical and Histological Study, *Quart. J. Med.* **24**:15, 1931.

6. Christian, H. A.: Diagnosis of Chronic Nonvalvular Heart Disease (Chronic Myocarditis), *New England J. Med.* **208**:574, 1933.

7. Graybiel, A., and Sprague, H. B.: Bundle-Branch Block; an Analysis of 395 Cases, *Am. J. M. Sc.* **185**:395, 1933.

8. Lewis, T.: Illustrations of Heart-Sound Records, *Quart. J. Med.* **6**:441, 1912-1913.

9. The meaning of this term is not always clear. Because the normal first sound does not begin until the beginning of systole, it is preferable to reserve the term "reduplicated first sound" or "double first sound" for those sounds which are entirely systolic in time, and to use the term "gallop rhythm" or "gallop sound" to describe the abnormal sounds which originate in diastole. This terminology will be used in this report. It is clear that King and McEachern⁴ regarded the signs which they found as being systolic. The terminology of gallop rhythm has been discussed by Holt (Gallop Rhythm, *Am. Heart J.* **2**:453, 1927) and by Wolferth and Margolies (Gallop Rhythm and the Physiological Third Sound: I. Characteristics of the Sounds, Classification, Comparative Incidence of the Various Types and Differential Diagnosis, *Am. Heart J.* **8**:441, 1933).

10. Lewis, T.: Lectures on the Heart, New York, Paul B. Hoeber, Inc., 1915, p. 53.

11. Battaerd, P. J. T. A.: Further Graphic Researches on the Acoustic Phenomena of the Heart in Normal and Pathological Conditions, *Heart* **6**:121, 1915.

in a number of patients with bundle branch block and stated that the sounds and their time relation to the electrocardiogram were normal. Wolferth and Margolies¹² reported the occurrence of a double first sound in the records obtained from one patient with bundle branch block. MacLeod, Wilson and Barker¹³ recorded the sounds in four patients with bundle branch block. The sounds were normal in one patient, but in the other three presystolic gallop rhythm was present. They pointed out that because of the time of occurrence of the extra sound it could not be attributed to asynchronism of the ventricles. These three observations bring the total number of records of abnormal sounds in bundle branch block to eight; in seven instances there was presystolic gallop rhythm.

Eppinger and Stoerk¹⁴ and Kauf¹⁵ reported the occurrence of a double systolic impulse in bundle branch block. Their records are not entirely convincing, however, and will be commented on later.

These observations indicate that abnormal physical signs are common in bundle branch block, but they leave some doubt as to their exact nature and diagnostic value. The present study was undertaken in an effort to obtain more information on these points by means of records of the heart sounds and apex cardiograms.

Twenty-three patients have been studied, twenty of whom had electrocardiograms fulfilling the criteria of Carter^{3a} for the diagnosis of bundle branch block. The electrocardiograms of the three remaining patients did not fulfil all these criteria, but in each case the Q R S complex measured 0.1 second or more. They are included in this study because King and McEachern² found that patients with this type of electrocardiogram often have physical signs similar to those present in patients with bundle branch block. With two or three exceptions all of the patients in the Stanford University Hospitals or in the outpatient service in the past four years who were found to have bundle branch block have been studied. Records of the heart sounds have been obtained from all patients; records of the apex beat, from fourteen. In seven of the first patients examined no attempt was made to record the apex beat, and in three others in whom the apex beat could not be seen or felt, attempts to record it were unsuccessful.

12. Wolferth, C. C., and Margolies, A.: The Various Types of Extra Heart Sounds, *M. Clin. North America* **14**:897 (Jan.) 1931.

13. MacLeod, A. G.; Wilson, F. N., and Barker, P. S.: Observations on the Heart Sounds with Particular Reference to Gallop Rhythm and Sounds of Auricular Origin, *Proc. Soc. Exper. Biol. & Med.* **29**:1009, 1932.

14. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiogramms, *Ztschr. f. klin. Med.* **71**:157, 1910.

15. Kauf, E.: Zur Diagnose des Schenkelblocks beim menschlichen Herzen, *Ztschr. f. klin. Med.* **98**:126, 1924.

METHODS

The records of the heart sounds were obtained by means of Frank's capsules by a method similar to that described by Wiggers and Dean.¹⁶ The capsule membranes were made of collodion or a similar material¹⁷ rather than of rubber. Electrocardiograms were made simultaneously with the records of the sounds. In each case the shadow of the galvanometer string and the beam of light from the sound capsule were photographed simultaneously on stationary paper to determine whether or not the two records were synchronous. This method has been satisfactory in recording abnormal sounds in a large number of patients. By recording the heart sounds and the electrocardiogram simultaneously, the exact time relations of the heart sounds to other events of the cardiac cycle can be determined.

Frank's capsules were also used to record the apex beat, but the capsule membrane was thicker and made of rubber, and the entire system from the receiver on the chest wall to the capsule was closed. Comparison of the time of the initial systolic deflection in the apex cardiogram with that of the Q R S complex does not reveal any marked delay. Apex cardiograms are not subject to exact interpretation, and their appearance in a given patient may be changed remarkably by slight changes in the position on the chest wall from which the records are obtained. However, in the majority of the records obtained from the patients in this group a relatively simple wave, for the most part positive (indicating an outward displacement of the chest wall beneath the receiver), was obtained from the position of maximum impulse. It seems reasonable to assume that such a record represents what one might feel as an impulse in that region.

RESULTS

The nature of the physical signs present in this series of patients, together with certain clinical data, is given in table 1. The patients are grouped according to the type of abnormal sign present.

In a few of the eight patients classified as having no abnormal physical signs small presystolic vibrations or small presystolic waves were recorded, but as these signs could not be detected on physical examination, these patients have not been classified with those having abnormal signs.

16. Wiggers, C. J., and Dean, A., Jr.: *The Principles and Practice of Registering Heart Sounds by Direct Methods*, *Am. J. M. Sc.* **153**:666, 1917.

17. The most satisfactory and durable membranes were made from Duco household cement thinned with amyl acetate. An exceedingly thin membrane can be made by dropping some of this material onto water.

The records obtained from three of the eight patients of this group are of interest because the sounds were recorded during bundle branch block and during cycles with a relatively normal Q R S complex. The

TABLE 1.—*Nature of the Records of the Heart Sounds and the Apex Cardiograms Obtained in Twenty-Three Patients with Bundle Branch Block*

Patient	Age	Sex	Rhythm	Blood Pressure	Heart Sounds	Apex Cardiogram
1*	48	M	Sinus	140/ 94	Normal	Normal
2	63	M	Sinus	184/120	Normal	Normal
3	58	M	Sinus	180/ 98	Normal	Normal
4	53	F	Sinus	170/110	Normal	Not recorded
5	58	M	Auricular fibrillation	230/120	Normal	Not recorded
6	60	M	Auriculoventricular block	144/ 90	Normal	Not recorded
7	80	F	Auriculoventricular block	220/ 88	Normal	Not recorded
8	64	M	Auricular fibrillation	124/ 74	Normal	Not recorded
9	50	M	Sinus	220/116	Presystolic gallop	Presystolic impulse
			Auricular fibrillation	200/110	Protodiastolic gallop	Protodiastolic impulse
10	44	M	Sinus	200/110	Presystolic gallop	Presystolic impulse
11	51	F	Sinus	160/ 92	Presystolic gallop	Presystolic impulse
12	60	F	Sinus	140/ 70	Presystolic gallop	Normal
13*	47	F	Sinus	142/ 84	Presystolic gallop	Normal
14	76	M	Sinus	170/100	Normal	Presystolic impulse
15*	51	M	Sinus	135/ 74	Presystolic gallop	Not recorded
16	60	F	Sinus	178/ 80	Presystolic gallop	Not recorded
17	60	F	Sinus	210/110	Presystolic gallop	Not recorded
18	50	F	Sinus	138/ 90	Double first sound	Normal
19	70	F	Auricular fibrillation	110/ 80	Double first sound	Normal
			Sinus	Double first sound	Normal
20	64	F	Sinus	140/ 80	Double first sound	Normal
21	60	F	Sinus	200/130	Double first sound	Normal
22	59	F	Sinus	170/ 86	Double first sound	Not recorded
23	69	M	Auriculoventricular block	210/ 90	Normal	Double systolic impulse

* "Atypical" bundle branch block.

records obtained from one of these patients are shown in figure 1. At the time these records were made many ventricular complexes occurred with a Q R S complex of normal duration, although several electrocardiograms made at other times were typical of bundle branch

block. The record shows that the amplitude of the vibrations of the first sound is less during bundle branch block than during the other cycles. This change was not always as marked as in the portion of the records shown, but it was always present to some degree. In the other two patients with changes in the form of the Q R S complex—a patient presenting heart block and cycles with a Q R S complex of normal duration mixed with those of bundle branch block and a patient presenting intermittent periods of bundle branch block—changes in the appearance of the records of the heart sounds did not accompany the changes in the electrocardiograms. Apex cardiograms were not obtained from these patients or from two others of this group. While these records are of interest and illustrate the fact that changes in the form of the Q R S complex do not necessarily produce important

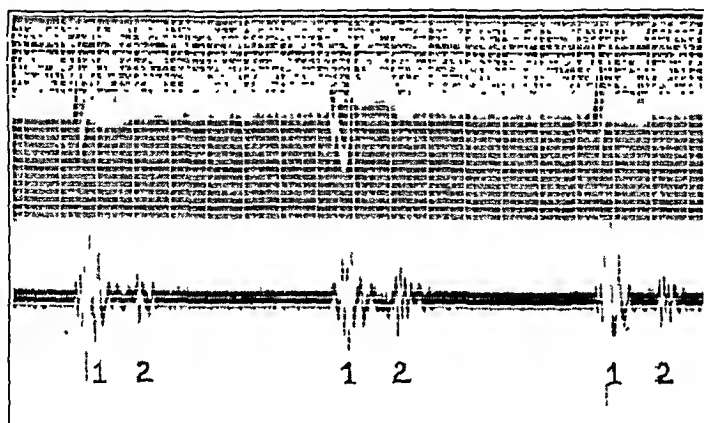


Fig. 1 (patient 5).—The second ventricular complex shown is that of bundle branch block and represents the usual type of Q R S complex present in this patient. The vibrations of the first sound accompanying this cycle are lower in amplitude than those of the other two cycles shown. These have a relatively normal Q R S complex.

changes in the character of the sounds, they have no particular bearing on the questions involved and need no further comment.

Examples of the records obtained from the nine patients with pre-systolic signs are shown in figures 2, 3, 4 and 5. The character of the sounds heard and the appearance of the records were similar, in the majority of patients, to the sounds heard and recorded in the usual patient with presystolic gallop rhythm. The only obvious difference between the records of gallop rhythm obtained from these patients and those obtained from patients without bundle branch block was the tendency for the sound responsible for the gallop to follow the P wave by a longer interval in the patients with bundle branch block, a point noted by T. Lewis⁸ in the records that he obtained from patients with this condition. The time relations of these sounds and corresponding

impulses to the P wave and the QRS complex are shown in table 2. The interval from P to the gallop sound, which ranged from 0.12 to 0.17 second, may be compared with an interval of from 0.08 to 0.14 second found by Wolferth and Margolies¹⁸ in a group of patients with presystolic gallop rhythm. Although this interval was often within

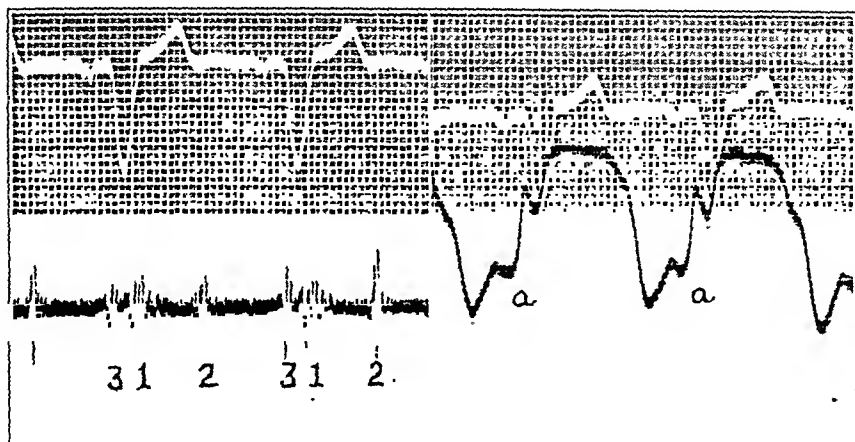


Fig. 2 (patient 9).—Presystolic gallop rhythm. The records of the heart sounds show a presystolic sound (3); the apex cardiograms, a presystolic impulse (a). (The gallop sounds and impulses will be indicated in the same manner in the records to follow.)

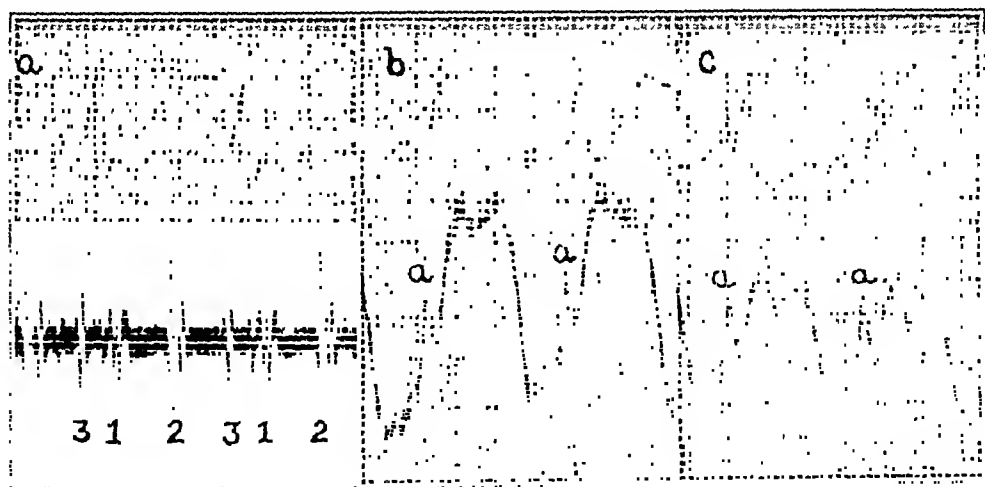


Fig. 3 (patient 10).—Presystolic gallop rhythm. Presystolic sounds and impulses are shown. The apex cardiograms in records *b* and *c* were obtained in adjacent areas. Those in record *c* show a double systolic wave in addition to the presystolic wave.

the range found by Wolferth and Margolies, in several patients it was considerably prolonged, so much so that the gallop sound preceded

18. Wolferth, C. C., and Margolies, A.: Gallop Rhythm and the Physiological Third Heart-Sound: I. Characteristics of the Sounds, Classification, Comparative Incidence of the Various Types and Differential Diagnosis, *Am. Heart J.* 8:441, 1933.

the initial deflection of the Q R S complex by less than 0.02 second. This was the case in patients 10 and 12 (figs. 3 and 4) and patient 16. The prolongation of this interval brought the presystolic sound close to the first heart sound and was probably the factor responsible for the clinical interpretation of the sounds shown in figure 4 as a reduplicated first sound rather than as gallop rhythm. In this record the interval from P to the gallop sound is 0.15 second, and the interval from the beginning of the presystolic sound to the first heart sound is 0.07 second. During the course of this study the same prolongation of this interval was found in a number of patients with gallop rhythm but without bundle branch block and was apparently responsible for the same error in the clinical interpretation of the physical signs. It should be noted that other factors may modify the effect of the lengthening of

TABLE 2.—*Time Relations Between the Presystolic Sounds and the Electrocardiogram*

Patient	Interval in Seconds Between			
	P and R	P and Gallop Sound	R and First Heart Sound	Gallop Sound and First Heart Sound
9.....	0.20	0.17	0.09	0.12
10.....	0.16	0.15	0.09	0.10
11.....	0.18	0.13	0.06	0.11
12.....	0.16	0.15	0.06	0.07
13*.....	0.20	0.15	0.05	0.10
14.....	0.20
15*.....	0.20	0.12	?	?
16.....	0.16	0.14	0.07	0.09
17.....	0.18	0.12	0.06	0.12

* "Atypical" bundle branch block.

this interval on the proximity of the sounds. For example, in figure 3 (patient 10) and in figure 5 (patient 13) the interval from P to the presystolic sound is also 0.15 second, but the interval between the initial deflection of the two sounds is 0.1 second (compared with 0.07 second in figure 4), and the sounds were interpreted clinically as presystolic gallop rhythm. In figure 5 the modifying factor is a prolongation of the P R interval, and in figure 3 it is a prolongation of the interval between the initial deflection of the Q R S complex and the first heart sound. Prolongation of this interval was also present in other patients with bundle branch block and was noted by T. Lewis.⁸ In this patient the interval was 0.09 second, considerably longer than that found in other persons by the same method.

Records of presystolic impulses are shown in figures 2 and 3 along with the corresponding records of the sounds. The impulses began earlier than the sounds, and in the patients in whom both sounds and impulses were present, the sounds occurred during the ascent or at the peak of the presystolic wave. The waves present in these records are

higher than those obtained in persons without palpable presystolic impulses, in respect both to their total height and to their height in proportion to that of the main systolic wave. This relation varied with

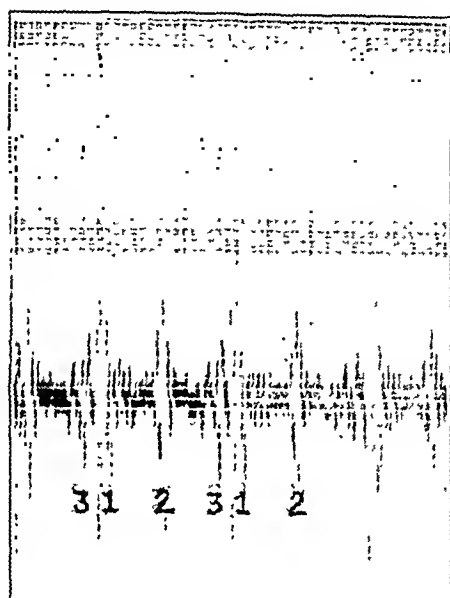


Fig. 4 (patient 12).—Presystolic gallop rhythm. The interval from the gallop sound to the first heart sound is short, measuring 0.07 second. The sounds heard were interpreted as a double first sound.

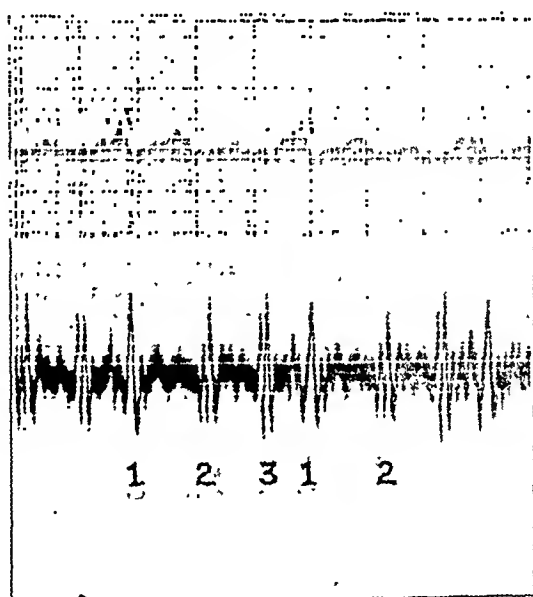


Fig. 5 (patient 13).—Presystolic gallop rhythm in a patient with "atypical" bundle branch block. Because of their low frequency, some of the vibrations of the first sound do not, in all probability, represent audible sound.

the position in which the record was obtained, a point illustrated by figures 3 *b* and *c*, but even in records showing the maximum systolic deflection obtainable in a given patient the height of the presystolic wave

may be almost one-half that of the main systolic wave. Such a record is shown in figure 3 *b*.

On palpation these impulses gave one the impression of an initial thrust, often abrupt, followed after a brief interval by a second more sustained rise. Some question may be raised as to the relation between the impulse felt and waves recorded in figure 3, since the records shown in figure 3 *c* show two systolic waves as well as a presystolic wave.

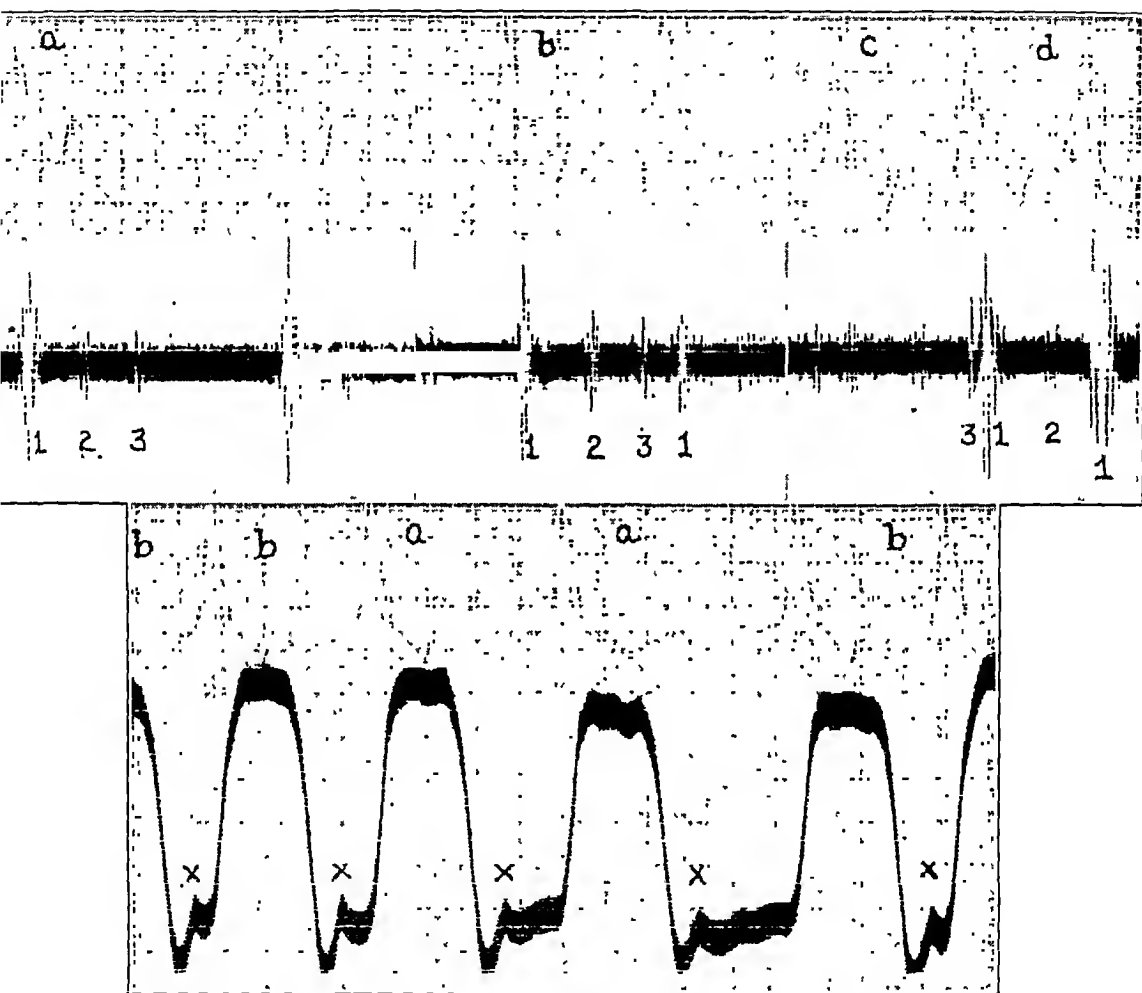


Fig. 6 (patient 9).—Protodiastolic gallop rhythm during auricular fibrillation. (Records obtained from this patient during sinus rhythm were shown in figure 2.) The protodiastolic sound (3) bears a definite relation to the preceding cycle. However, its relative position in the cardiac cycle depends on the length of diastole. In the long diastole of cycle *a* its position is that of a protodiastolic gallop sound, but in the shorter diastole of cycle *b* it occupies the position of a presystolic gallop sound. Cycles *c* and *d* are still shorter. In *c* the gallop sound (3) occurs after R but before the first sound of the following cycle; in *d*, in which the time of occurrence of the gallop sound and of the first heart sound of the following cycle are approximately the same, the first heart sound is exaggerated. The apex cardiograms show protodiastolic waves (*x*) which occur at approximately the same time as the protodiastolic sounds.

However, the fact that the presystolic wave is more prominent than the two systolic waves, together with the fact that the physical signs resembled those present in the other patients of the group, leads one to believe that the presystolic wave was the extra impulse felt. Records similar to this were not obtained in any other patient of this group.

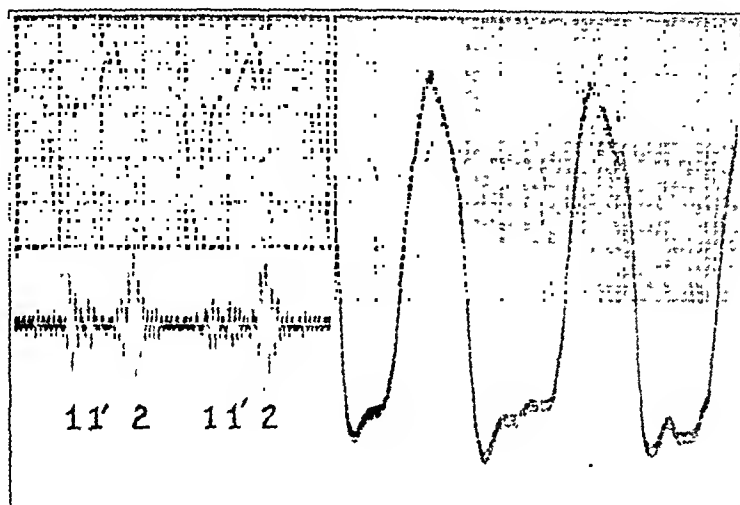


Fig. 7 (patient 19).—The records of the heart sounds show a double first sound (1 1'). The apex cardiograms are not remarkable. Records obtained from this patient during sinus rhythm also showed a double first sound.

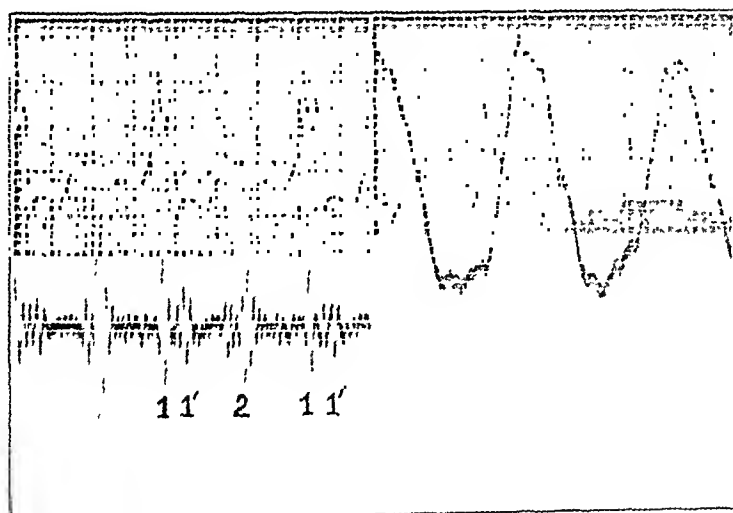


Fig. 8 (patient 20).—The records of the heart sounds show a double first sound (1 1') and a double second sound (2). The apex cardiograms are not remarkable.

The changes which took place in the physical signs presented by patient 9 following the onset of auricular fibrillation are of sufficient importance to warrant a more detailed description. The records obtained from this patient before the change in rhythm are shown in figure 2. Similar records were obtained on five occasions covering a period of three years, the last being made two weeks before the onset of fibrillation and a month before the records shown in figure 6 were obtained.

In these records the presystolic sounds and impulses have disappeared and are replaced by protodiastolic sounds and waves. These are protodiastolic in the sense that they bear a definite time relation to the preceding cycle; actually they may fall in any part of a diastole. In a long diastolic pause, such as is present in cycle *a* of the sound and apex cardiogram tracings, the sound and impulse occur in early diastole, but during shorter cycles, such as *b*, they occur close to the first sound at about the time in the cardiac cycle that presystolic sounds and impulses occur. In cycle *c* of the sound record the protodiastolic sound actually begins after the R wave of the following cycle, and in cycles such as *d*, in which the time occurrence of the protodiastolic sound and wave is about the same as that of the first heart sound, the first heart sound is exaggerated just as it is in heart block when auricular and ventricular systole are close together. The interval from R to the protodiastolic

TABLE 3.—*Time Relations Between the Double First Sound and the Electrocardiogram*

Patient	Interval in Seconds Between	
	R and First Component of Sound	R and Second Component of Sound
18.....	0.07	0.15
19.....	0.08	0.19
20.....	0.08	0.17
21.....
22.....	0.04	0.11

sound varies from 0.65 to 0.7 second, with an average of 0.67 second, and the interval from R to the peak of the protodiastolic wave varies from 0.66 to 0.73 second, with an average of 0.69 second. The variation in this interval in different cycles depends, in part, on the length of the preceding cycle, the interval being shorter if the preceding cardiac cycle was shorter. This relation was noted by Wolferth and Margolies¹⁸ in the records of sounds which they obtained from a patient with auricular fibrillation and gallop rhythm. Exaggeration of the first sound was present when it occurred from 0.62 to 0.67 second after the R wave of the preceding cycle. It seems likely that the variations in these intervals would be less if the measurements of both sounds and waves could be made from the same cycle, but it was not possible to obtain records of the sounds and apex cardiograms simultaneously.

The sounds heard in patient 9 were somewhat confusing. During long diastolic pauses the sounds could be identified as protodiastolic, but during shorter pauses one often got the impression of hearing a double first sound. The wave was not palpable.

The records obtained from two of the five patients with double first sounds are shown in figures 7 and 8. The sounds could be heard and recorded best along the left sternal border in the third or fourth intercostal space. In two patients the second heart sound was double. In the patient whose records are shown in figure 7 a change in rhythm from auricular fibrillation to sinus rhythm was not accompanied by a change in the character of the sound. In one of the patients included in this group a record of what appeared to be a double first sound was obtained, but an electrocardiogram was not made simultaneously with the records of the heart sounds. Two days later, when both records were taken simultaneously, the double first sound was absent, but as the total interval from the beginning of the first sound to the end of the second sound was the same on both occasions, it was concluded that the double sounds recorded in the first records were systolic.

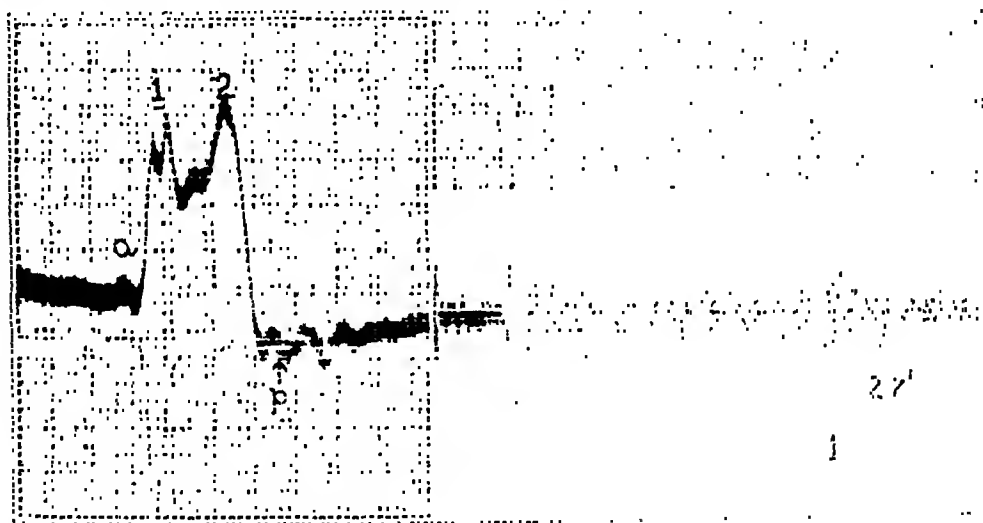


Fig. 9 (patient 23).—The apex cardiogram shows a double systolic impulse in which the first element is split. The auricular impulse (*a*) corresponding to the P wave immediately before the ventricular complex is separate from the systolic impulses. The next auricular wave cannot be identified, but the location of the corresponding P wave (determined by measuring the interval between the P waves on each side of the preceding ventricular complex) shows that it is also separate from the systolic impulses. The records of the heart sounds show an exaggerated first sound and a double second sound in the second cycle.

The time relations between the reduplicated sounds and the electrocardiogram are shown in table 3. In three patients the first element of the double sound occurred somewhat later in relation to the QRS complex than the normal first heart sound. The two components of the double first sound began at an interval of from 0.7 to 0.11 second.

Double systolic impulses were not present in any of the four apex cardiograms obtained from the patients with reduplicated first sounds. The apex cardiograms obtained from two of them are shown along with the records of the sounds in figures 7 and 8.

The records shown in figure 9 are the only ones obtained showing a double systolic impulse. The electrocardiogram is that of complete heart block and bundle branch block of the rare form with a Q R S complex of 0.18 second. The first element of the double impulse, which is split, begins 0.04 second after the initial deflection of the Q R S complex, but the main rise of the second portion of the impulse does not begin until 0.12 second after the end of the Q R S complex. The auricular waves were palpable in this person, but in the cycle shown the auricular waves which precede and follow this particular ventricular beat are separate and therefore play no part in the production of the double impulse. The records of the sounds of this patient, also presented in figure 9, show an exaggeration of the first sound when P falls near the Q R S complex and a double second sound.

COMMENT

The records obtained from this group of patients show clearly that abnormal physical signs of two distinct types may be found in patients with bundle branch block. Although the group of patients studied is not large, both types of abnormal signs occurred with sufficient frequency to indicate that their presence is in some way related to bundle branch block or to the type of heart disease in which it occurs.

The presystolic signs cannot be due, as MacLeod, Wilson and Barker¹³ pointed out, to asynchronism of the ventricles (or to bundle branch block itself), since they occur before the beginning of ventricular systole. The resemblance of the records of presystolic sounds and impulses obtained in these patients to those obtained in patients with gallop rhythm but without bundle branch block, their relation to auricular systole as shown by the relation of the sounds and impulses to the P wave of the electrocardiogram and the disappearance of the presystolic gallop sound and impulse shown in figure 6 following the onset of auricular fibrillation leave no doubt that these signs are of the same nature and are produced in the same manner as the presystolic gallop rhythm which occurs in patients without bundle branch block. The mechanism by which gallop sounds are produced has been adequately considered by T. Lewis,¹⁰ Mond and Oppenheimer¹⁹ and Wolferth and Margolies.¹⁸ All that need be stated here is that according to their views the event which leads to the production of presystolic gallop sounds is auricular systole.²⁰ T. Lewis¹⁰ and Wolferth and Margolies¹⁸ have suggested that the corresponding event which leads to

19. Mond, H., and Oppenheimer, E. T.: Gallop Rhythm in Hypertension, *Arch. Int. Med.* **43**:166 (Feb.) 1929.

20. A logical explanation of the mechanism by which auricular systole leads to the production of sound will be found in the paper by Mond and Oppenheimer.¹⁹

the production of protodiastolic sounds is the rise in intraventricular pressure which occurs early in diastole. The close relation of the protodiastolic wave to the other events of the cardiac cycle and to the protodiastolic sound which is present in figure 6 during auricular fibrillation suggests that this wave represents this early diastolic rise in intraventricular pressure and supports the views of the authors just mentioned as to its relation to the production of protodiastolic sounds. Further evidence that the protodiastolic wave is related to sound production in the same way as auricular systole is provided by the exaggeration of the first heart sound when the wave (or the protodiastolic sound) and the first heart sound of the following cycle occur close together (figure 6, cycles *d*), an effect which is similar to the exaggeration of the first sound which occurs in heart block when auricular systole occurs close to the first sound.

As presystolic gallop rhythm cannot be produced by bundle branch block itself, some other reason must be sought not only for its presence but for the frequency with which it was found in this group of patients. Its occurrence in nine of twenty-three patients (seven of twenty if those with "atypical" bundle branch block are excluded) is a higher incidence than one would expect in an unselected group of patients with degenerative heart disease. The frequency with which it occurred may be compared with its presence in twelve of one hundred consecutive patients with cardiac disease examined by King and McEachern.² None of these twelve patients had bundle branch block. This observation is more remarkable if the degree of cardiac failure present is considered. Gallop rhythm is most frequently associated with advanced or acute stages of cardiac insufficiency, but in this particular group only one of the nine patients had definite congestive failure at the time of examination. All of the remaining patients had other evidence of heart disease, and several had experienced attacks of congestive failure, but all were ambulatory at the time of examination. The frequency with which White⁴ found interventricular block in a group of patients with gallop rhythm also indicates that it is unusually common in this condition, but the significance of his findings in this connection may be questioned since he found protodiastolic gallop rhythm in the majority of his patients. Further comment in regard to the type of gallop rhythm will be made later.

The fact that gallop rhythm occurs in some patients with bundle branch block is reasonably explained by the similarity of the conditions with which these anomalies are associated. Gallop rhythm, in all probability, does not occur without definite impairment of cardiac function, and it is usually found in persons with degenerative heart disease, often with marked hypertension. Bundle branch block is also found, as a rule, in patients with degenerative heart disease, and while it may

occur in persons with good cardiac function it is almost always associated with other definite evidence of heart disease. No doubt marked hypertension favors the development of gallop rhythm, but it is by no means essential. A number of records of gallop rhythm have been obtained in this laboratory from persons with normal blood pressure, and it is a well known occurrence in patients with coronary occlusion and low blood pressure. It is not surprising, therefore, to find that a certain number of patients with bundle branch block and evidence of cardiac insufficiency have gallop rhythm. This explanation is adequate to account for the presence of gallop rhythm in a certain number of patients, but one cannot be certain that it accounts entirely for the unusual frequency with which it was found. It is possible that this finding is related to the severity of the heart disease associated with bundle branch block, a fact which is emphasized by the poor prognosis found in persons with bundle branch block by Willius,²¹ Graybiel and Sprague⁷ and others.

The fact that presystolic gallop rhythm was the type present in the records of all but one of the patients with gallop rhythm in this series and in all of the other records of gallop rhythm obtained in this condition should be noted, since the protodiastolic and the presystolic type appear to be of about the same significance and to occur with about the same frequency.¹⁸ There is no obvious explanation for this observation. However, the fact that White⁴ found protodiastolic gallop rhythm to be the most common form suggests that a larger series of records would show a more equal distribution of the type of gallop rhythm present. Although White's observations were based on clinical evidence alone and were therefore subject to error, since it is often difficult to distinguish between the two common forms of gallop rhythm without records of the sounds, it is likely that the majority of his observations were correct.

The late occurrence of the gallop sound in relation to the P wave noted by T. Lewis⁸ and present in some of the records obtained from this group of patients also requires some comment. A complete explanation for this fact is not apparent, but the observations of Duchosal²² on factors influencing this interval should be mentioned. He found that as the degree of heart failure became less, the interval from P to the gallop sound increased. The same relation appears to exist in this series of patients, since only one was suffering from a severe degree of congestive failure at the time of examination. However, the data obtained were not entirely comparable, since well marked changes in

21. Willius, F. A.: Arborization Block, *Arch. Int. Med.* **23**:431 (April) 1919.

22. Duchosal, P.: A Study of Gallop Rhythm by a Combination of Phonocardiographic and Electrocardiographic Methods, *Am. Heart J.* **7**:613, 1932.

the state of cardiac function did not occur during the period of observation, nor were there sharp differences in the degree of cardiac failure among persons of this group. The single patient with congestive failure had only a presystolic impulse.

A reduplicated first sound has been noted under various circumstances, and Wohlers and Duchosal²³ recorded it in a number of patients, but it does not appear to have been associated with any particular condition. Consequently, its demonstration in five patients with bundle branch block and the close time relations of the sounds and the Q R S complex in these patients suggest that the two are definitely related or, more specifically, that the reduplicated sound is due to asynchronism of the ventricles. However, sufficient data to show that asynchronism of the ventricles is present in bundle branch block or that it is accompanied by a reduplicated sound are not available. Eppinger and Rothberger²⁴ found a difference of 0.04 second in the time of onset of the pulse wave in the aorta and in the pulmonary artery after cutting one branch of the His bundle in the dog. On the other hand, Katz²⁵ found almost as great a degree of asynchronism (0.035 second) in the beginning of ventricular systole under ordinary experimental conditions. Wiggers²⁶ found still greater degrees of asynchronism in ventricular extrasystole, a condition which is not accompanied by reduplicated sounds. In three experiments made in this laboratory the sounds were recorded directly from the heart after the cutting of the right bundle branch. Although the number of experiments was too small to lead to any definite conclusion, the fact that a double first sound did not occur is worth mentioning.

The single record of a double systolic impulse does not provide sufficient evidence on which to base a discussion concerning the nature of this particular sign. The significance of the record might also be questioned because of the other unusual features present, namely, heart block and an unusually wide Q R S complex.

The recognition of the fact that abnormal signs were present was not difficult, but in some cases errors were made in the interpretation of the kind of abnormality. Occasionally presystolic gallop rhythm

23. Wohlers, H., and Duchosal, P.: *Etude phonocardiographique des dédoublements du premier bruit du coeur*, Arch. d. mal. du coeur **25**:1, 1932.

24. Eppinger, H., and Rothberger, J.: *Ueber die Sukzession der Kontraktion der beider Herzkammern, insbesondere nach einseitiger Blockierung der Erregungsüberleitung*, Zentralbl. f. Physiol. **24**:1055, 1910.

25. Katz, L. N.: *The Asynchronism of the Right and Left Ventricular Contractions and the Independent Variations in Their Duration*, Am. J. Physiol. **72**: 655, 1925.

26. Wiggers, C. J.: *The Muscular Reactions of the Mammalian Ventricle to Artificial Surface Stimuli*, Am. J. Physiol. **73**:346, 1925.

was interpreted as protodiastolic gallop. The interpretation of presystolic gallop rhythm as a reduplicated first sound, which was made in patient 12 of this series and in a number of patients without bundle branch block, has already been commented on. It is probable that in these persons the judgment as to the time of occurrence of the abnormal sounds was influenced by the character of the sounds heard rather than by actual timing with other events of the cardiac cycle. The presystolic impulses were interpreted correctly, but it seems likely that this interpretation was influenced by the belief that a presystolic sound was present. In the patient in whom a double systolic impulse occurred, there was some doubt as to its exact nature because of the presence of palpable auricular impulses. However, the apex cardiograms showed that these played no part in the production of the double systolic impulse.

It is apparent from the nature and the difference in type of the abnormal physical signs found in the records obtained from this group of patients that such signs are not suitable for use as evidence of bundle branch block. Presystolic gallop rhythm, which made up over one half of the abnormal physical signs, cannot be related to bundle branch block. Its presence is determined largely by the state of cardiac function and the type of heart disease, not by the presence of bundle branch block. Although the gallop rhythm differs in some respects from that usually encountered, these differences are not necessarily related to bundle branch block, nor can they be easily recognized on physical examination. A reduplicated first sound might appear to be of some value as a physical sign because it is possible that it has a direct relation to bundle branch block and is not associated with any other condition. However, the frequency with which it occurs does not seem sufficient to warrant its use as an important diagnostic sign, and its usefulness is further reduced by the fact that it may occur under other circumstances or may be confused with presystolic gallop rhythm. The abnormal impulses in our patients were of little use as diagnostic signs. The presystolic impulses which accompanied presystolic sounds in a few cases have the same significance as the sounds, and the occurrence of a double systolic impulse but once in fourteen patients in this group does not warrant its consideration as a specific physical sign.

A comparison of the physical signs found by King and McEachern² with those found in this group of patients reveals marked differences. Reduplicated first sounds were noted in both series, but presystolic gallop rhythm, which was the predominant finding in our group of patients, was not noted by them, and a double systolic impulse, which was the most frequent sign found in their patients, could be demonstrated in but one of fourteen patients in our series. These differences are sufficiently marked to justify further comment.

The frequency with which presystolic gallop rhythm was demonstrated by records of the heart sounds in this group of patients, as well as its occurrence in seven of the eight records of abnormal sounds previously obtained in cases of bundle branch block (Lewis,⁸ Wolferth and Margolies,¹⁸ MacLeod and his co-workers¹³), provides definite evidence that this sign is rather common in persons with this condition. No doubt the frequency with which it occurs in a group of patients is influenced by other factors, particularly the degree of heart failure present, but it is unlikely that it is entirely absent in any large group of persons with bundle branch block. For this reason it seems possible that King and McEachern² interpreted presystolic gallop rhythm as a reduplicated first sound in some of their patients. The factors which may lead to such an error have already been commented on.

The occurrence of presystolic impulses in this series was not remarkable since impulses of this kind are well known in patients with gallop rhythm and are, in all probability, a part of the same phenomenon. In regard to the failure to find double systolic impulses more frequently, all that can be said is that by a method which was capable of demonstrating abnormal impulses in a number of persons a double systolic impulse could be recorded in only one of fourteen patients. In addition, it may be pointed out that some of the evidence brought forth to show the presence of a double systolic impulse is not entirely satisfactory. The records published by Eppinger and Stoerk¹⁴ show three systolic waves, one rather high, and in several cycles a fourth wave, presystolic in time, which is about the same height as the small systolic waves. In view of the number of waves present and of the presence of a presystolic wave the use of this record as evidence of a double systolic impulse does not seem justifiable. The records published by Kauf¹⁵ were made with a Jacquet sphygmograph, a device generally regarded as inadequate to record the form of such an impulse as the apex beat. The evidence which King and McEachern² obtained by taking motion pictures of the shadow of a straw attached to the apex beat is not conclusive since it does not afford a means of determining the time in the cardiac cycle at which the various impulses occur. This criticism does not apply to the evidence that they obtained by photographing the shadow of the straw simultaneously with the taking of the electrocardiogram. However, the interpretation of one of the records obtained in this manner is open to criticism. In this record (fig. 5 of their paper) the second component of an impulse interpreted as a double systolic impulse begins well after the T wave of the electrocardiogram but before the P wave and is therefore a diastolic event, unrelated to auricular systole. This record is also quite different from the other records of double systolic impulse which were shown in their paper. In these records (figs. 5 and

6 of their paper) the two impulses originate in systole. It is possible that the second impulse shown in figure 5 of their paper represents the impulse of protodiastolic gallop rhythm.

As additional evidence to support their conclusions concerning the nature of the physical signs, King and McEachern² cited the occurrence of double systolic impulses in heart block and auricular fibrillation as evidence that the impulses present in their patients were not related to auricular systole and were, therefore, a different phenomenon than presystolic gallop rhythm. It is obvious that this is true, and it is supported, in the case of heart block, by the demonstration of a double systolic impulse quite separate from the auricular impulses shown in the records in figure 6 of their paper, as well as in the records in figure 9 of this report. However, the record first commented on (fig. 5 of their paper) shows that an impulse can occur in diastole, unrelated to auricular systole, and be interpreted clinically as part of the double systolic impulse. It is possible that the protodiastolic wave present during auricular fibrillation shown in figure 6 of this paper represents a similar event. Although this wave was not demonstrable on physical examination in this instance, it is conceivable that it might become visible or palpable under other circumstances, such as, for example, a more severe degree of heart failure, and become subject to the same error in interpretation. The various positions which the protodiastolic sound occupied, particularly its position close to the first sound in cycles such as *c* in figure 6, indicate that it might easily be interpreted as a part of a reduplicated first sound.

While the foregoing comments concerning the difference in the character of the apex beat found in the two series of patients do not imply that the observations of King and McEachern are entirely erroneous, they cast considerable doubt on their conclusion that all of the abnormal impulses which they observed were systolic.

SUMMARY

The nature of the physical signs present in twenty patients with bundle branch block and in three patients with "atypical" bundle branch block has been determined by means of records of the heart sounds and apex cardiograms. Records of the heart sounds were obtained from all patients; apex cardiograms, from fourteen.

Physical signs of two distinct types occurred.

Presystolic gallop rhythm was present in nine patients. In three of these patients a presystolic impulse was associated with the presystolic sound; in one the impulse was the only sign present.

A reduplicated first sound, entirely systolic, occurred in five patients. A double systolic impulse was present in one patient. A reduplicated

first sound and a double systolic impulse were not found together in any of the patients studied.

The presystolic gallop rhythm present in these patients was the same as that found in persons without bundle branch block except for a tendency for the interval between the P wave and the gallop sound to be prolonged. The lengthening of this interval may be related to the absence of severe grades of circulatory failure in this particular group at the time of examination. The presence of gallop rhythm in bundle branch block could be accounted for by the fact that both conditions occur in the same general type of heart disease and under the same circumstances. It could not be related to the bundle branch block itself (or to asynchronism of the ventricles).

The incidence of gallop rhythm in the whole group was higher than that present in an unselected group of patients with degenerative heart disease. The explanation for this fact was not entirely clear, but the frequency of the anomaly appeared to be a reflection of the severity of the heart disease which accompanies bundle branch block.

The frequency with which a reduplicated first sound occurred and its close association with the Q R S complex suggest that it may be produced by asynchronism of the ventricles. However, evidence to prove or disprove this point did not appear to be adequate.

The nature of the physical signs present was not such as to permit their use as diagnostic signs of bundle branch block.

Dr. Garnett Cheney and Dr. William Dock provided several of the patients included in this study.

BLOOD CHOLESTEROL AND THYROID DISEASE

III. MYXEDEMA AND HYPERCHOLESTEREMIA

LEWIS M. HURXTHAL, M.D.

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Numerous observations on the blood cholesterol in thyroid disease have been made and reported in the literature. References to the more important of these were included in a previous communication from the Lahey Clinic.¹ Since then reports of further investigations have appeared; yet in most of these a relatively small number of cases have been studied and fewer still have been followed from time to time.

Levy² followed the variations in the blood cholesterol in exophthalmic goiter treated by roentgen rays, and found variable results. Of ten cases, however, six showed a cholesterol value of more than 230 mg. per hundred cubic centimeters. Such findings seem unusual, because in this study less than 1 per cent of the patients with exophthalmic goiter were found to have a cholesterol value of this magnitude. Hilman³ concluded, as did Epstein,⁴ that hypercholesteremia was definite evidence against exophthalmic goiter, but that there was no rule regarding the behavior in that disease. The latter conclusion was also drawn by Bonilla and Maya.⁵ Epstein and Lande's⁴ observations on the blood cholesterol in thyroid disease and other diseases have apparently received scant attention in this country, but they are referred to frequently in French publications on the subject.

The effect of administering desiccated thyroid on the blood cholesterol has been the subject of more recent observations. The drop in cholesterol and the rise in the basal metabolic rate in myxedema follow-

From the Medical Department of the Lahey Clinic and the Chemical Laboratory of the New England Deaconess Hospital.

1. Mason, R. L.; Hunt, H. M., and Hurxthal, L. M.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism: Their Significance, *New England J. Med.* **203**:1273 (Dec. 25) 1930.

2. Levy, M.: The Variations in the Cholesterol in Basedow's Disease, Treated by Radiotherapy, *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:1844 (Dec. 14) 1931.

3: Hilman, M. L.: Cholesterolaemia in a Few Diseases of the Endocrine Glands, *Vrach. delo* **14**:13 (Jan.) 1931.

4. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: I. The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, *Arch. Int. Med.* **30**:563 (Nov.) 1922.

5. Bonilla, E., and Maya, A.: Der Wert Cholesterinämia in den Schilddrüsenerkrankheiten, *Endokrinologie* **9**:171 (Sept.) 1931.

ing the use of thyroid was described first by Luden,⁶ in 1918. Experimental work with animals confirmed earlier observations¹ that the cholesterol of the blood is decreased by the administration of either desiccated thyroid or thyroxine.⁷ Eleven cases of myxedema were reported by me in collaboration with Hunt and Mason,¹ and the return of the blood cholesterol to normal with thyroid therapy was shown. Parhon and Ornstein⁸ and Levy and Levy,⁹ on the basis that the blood cholesterol is elevated in old age and arteriosclerosis,¹⁰ treated patients for hypercholesteremia with thyroxine and claimed dramatic results. Apparently they entertained the belief that hypercholesteremia is a precursor of arteriosclerosis, but they apparently did not attribute this necessarily to thyroid deficiency. Higher cholesterol values were reported by Bloor, Buckner and Gibbs¹¹ for diabetic patients who show advanced arteriosclerosis, although this relationship was not found by Hunt.¹² High cholesterol values have been reported in arteriosclerosis without diabetes.¹³

A study of the blood cholesterol in mental disease has been made by several observers.¹⁴ Apparently the incidence of hypercholesteremia

6. Luden, G.: Studies on Cholesterol: V. The Blood Cholesterol in Malignant Disease and Effect of Radium on the Blood Cholesterol, Collected Papers, Mayo Clinic, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 470.

7. (a) Westra, J. J., and Kunde, M. M.: Blood Cholesterol in Experimental Hypo- and Hyperthyroidism, *Proc. Soc. Exper. Biol. & Med.* **29**:677 (May) 1932. (b) Simonds, J. P., and Helpler, O. E.: Fat Tolerance in Experimental Hyperthyroidism, *J. A. M. A.* **98**:283 (Jan. 23) 1932.

8. Parhon, C. I., and Ornstein, I.: Influence of Thyroxin on Cholesterol and Lipaemia, *Compt. rend. Soc. de biol.* **108**:303 (Oct. 16) 1931.

9. Levy, M., and Levy, E.: Thyroxin Therapy of Hypercholesterolaemia, *Presse méd.* **40**:240 (Feb. 13) 1932.

10. Parhon, C. J., and Parhon, M.: Hypercholesterolaemia of the Aged, *Compt. rend. Soc. de biol.* **88**:231, 1923.

11. Bloor, W. R.; Buckner, E., and Gibbs, C. B.: Cholesterol Ester in Diabetic Plasma, *Proc. Soc. Exper. Biol. & Med.* **30**:63 (Oct.) 1922.

12. Hunt, H. M.: Cholesterol in Blood of Diabetes Treated at New England Deaconess Hospital, *New England J. Med.* **201**:659 (Oct. 3) 1929.

13. Mjassnikow, A. L.: Cholesterol in Arteriosclerosis, *Ztschr. f. klin. Med.* **102**:65 (Aug.) 1925.

14. (a) Forsyth, W. L.: Hypocholesterolaemia in Dementia Praecox, *J. Ment. Sc.* **72**:219, 1926. (b) Schube, P. G.: Blood Cholesterol Studies in Mental Disease, *Am. J. Psychiat.* **12**:355 (Sept.) 1932. (c) Duncan, A. G.: The Serum Cholesterol in Mental Disorders, *J. Ment. Sc.* **76**:284 (April) 1930. (d) Shaw, B. H., and Sharpe, J. S.: The Significance of Cholesterol in Cellular Oxidation and Its Bearing on Mental Disorder, *J. Ment. Sc.* **77**:53 (Jan.) 1931. (e) Grabfield, G. P., and Campbell, A. G.: A Note on the Relation Between Blood Cholesterol and Basal Metabolic Rate, *New England J. Med.* **205**:1148 (Dec. 10) 1931. (f) Targowla, Badonnel, Berman: Cholesterolaemia in Mental Disease, *Encéphale* **18**:139, 1923. (g) Duncan, A. G.: Effect of Thyroid Administration on the Blood Cholesterol, *J. Ment. Sc.* **77**:332 (April) 1932.

is greater in mental than in general disease, although Looney¹⁵ believed otherwise. The effect of the administration of thyroid on the cholesterol was studied by Duncan,^{14g} and here again a marked drop was noted by him in all cases. Only two cases of twenty-two studied by him showed hypercholesteremia. Grabfield and Campbell^{14e} stated that the blood cholesterol is a function of neither the basal metabolic rate nor thyroid activity.

High cholesterol values are reported in such rare conditions as xanthomatosis, Niemann-Pick's disease and Christian-Schüller's disease.¹⁶ Desiccated thyroid, combined with anterior pituitary substance, was used in one case of Christian-Schüller's disease, with remarkable results.¹⁶ In view of the usual ineffectiveness of the oral administration of anterior pituitary substance, it is likely that the result was brought about by desiccated thyroid.

Hypercholesteremia was observed by Tolstoi¹⁷ in studies of the effect of a diet of meat and fat. Bloor, I believe, observed hypocholesteremia in two dogs fed a purely carbohydrate diet but he was unable to reproduce the findings.

Obstruction of the common bile duct by stone was found by Epstein¹⁸ to give high values for blood cholesterol, and this has been confirmed in six cases by Wilkinson and me in the Lahey Clinic.

RESPONSE OF THE BLOOD CHOLESTEROL TO THE ADMINISTRATION OF THYROID IN NORMAL PERSONS

As stated earlier, the blood cholesterol is lowered on the administration of thyroid substance. In table 1 are shown the results obtained in giving thyroid to three subjects: one with a low normal, one with an approximately average normal and one with a high normal cholesterol level.

POSTOPERATIVE FINDINGS

Typical postoperative myxedema is accompanied by hypercholesteremia. In almost every instance this means the finding of a cholesterol level of 230 mg. or more (or whatever the upper limit of normal is considered to be in a given laboratory). Occasionally, because of the wide range of cholesterol values for apparently normal persons, there may be found a person with undoubted myxedema and a blood chole-

15. Looney, Joseph: Personal communication to the author.

16. Lowland, R. S.: Lipoid Metabolism, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1920-1921, vol. 4, p. 214.

17. Tolstoi, Edward: The Effect of an Exclusive Meat Diet on the Chemical Constituents of the Blood, *J. Biol. Chem.* **83**:753 (Sept.) 1929.

18. Epstein, E. C.: Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, *Arch. Int. Med.* **50**:203 (Aug.) 1932.

terol level in the upper range of normal (from 200 to 230 mg. per hundred cubic centimeters). In myxedema, however, the per cent of increase in the blood cholesterol as a result of thyroid deficiency is, on the average, so much greater than the per cent of decrease in the basal metabolic rate that the cholesterol stands out in contrast to the metabolism as an indicator of thyroid deficiency. Hypometabolism is not an invariable finding in myxedema, and furthermore, it is frequently found in other conditions. Hypercholesteremia, on the other hand, is a relatively uncommon finding except in such obvious clinical conditions as diabetes, nephrosis, obstruction of the common duct and, perhaps, advanced arteriosclerosis.

TABLE 1.—*Effect of Administration of Thyroid on Blood Cholesterol in Three Apparently Normal Persons*

Time, Weeks	Basal Metabolic Rate, per Cent	Cholesterol, Mg. per 100 Ce.	Pulse Rate	Weight, Pounds	Thyroid
Housewife, Aged 29					
5 days	—35, —37	133	84	146.5, 146	Started with 4 grains
4	—18	70	84	135	Reduced to 2 grains
2	+12	104	84	131	Reduced to 1 grain
Physician, Male, Aged 36					
	—16	160	57	152.5	Started with 2 grains
8	—13	128	64	150.2	Started with 4 grains
4	— 8	108	74	151.2	Stopped at 4 grains
4	—17	154	58	149	
Technician, Female, Aged 28					
	— 7	230	..	180	Started with 2 grains
2	+ 4	150	..	178	Stopped at 2 grains
2	—10	235	..	180	

POSTOPERATIVE HYPOMETABOLISM WITHOUT HYPERCHOLESTEREMIA

In chart 1 are shown findings in seventy-eight postoperative cases with metabolic rates of —10 per cent or lower and cholesterol values below 200 mg. Most of the patients showed no clinical evidence of thyroid deficiency, although some had suggestive signs. In the beginning, desiccated thyroid (usually 2 grains [0.13 Gm.], U. S. P., a day) was prescribed without knowledge of the cholesterol value, when it was felt that thyroid might be of benefit. In most instances, the results of treatment were doubtful or negative in cases in which the cholesterol value was below 200 mg. One case of undoubted postoperative clinical myxedema showed a cholesterol value of 198 mg.; after treatment, the cholesterol fell to 120 mg. In prescribing thyroid, it has been my experience that most patients will discontinue it if it has not been helpful. On the other hand, it is not uncommon for them to discontinue it even if benefit has resulted, but they either will resume it on their own volition

or will agree that it produced improvement. It is largely by this means that results of the administration of thyroid have been evaluated in these postoperative cases.

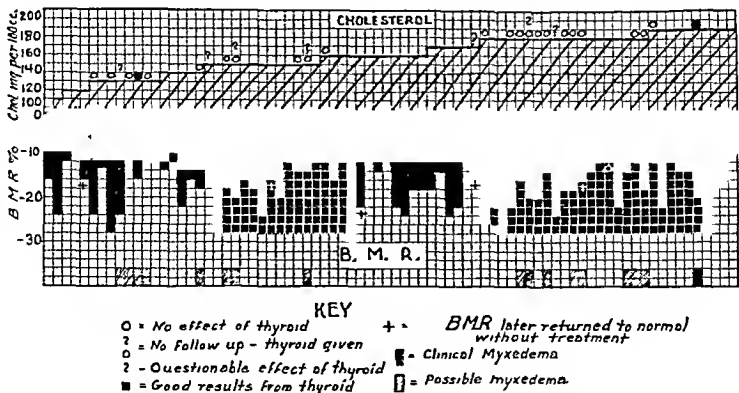


Chart 1.—Data on cases of postoperative thyroid disease with low metabolic rates and blood cholesterol of less than 200 mg. Note the infrequency of clinical myxedema as well as beneficial effects of the administration of thyroid.

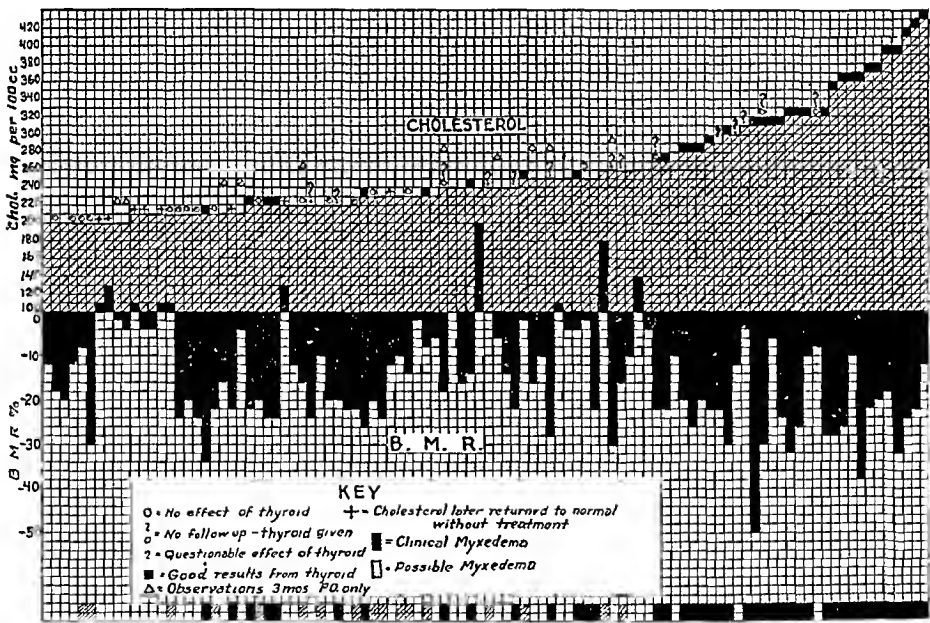


Chart 2.—Data on cases of postoperative thyroid disease with cholesterol over 200 mg. regardless of the basal metabolic rate. Note the increasing frequency and severity of clinical myxedema as higher cholesterol values are reached. Note the variability of the basal metabolic rates which were observed after a night's stay in the hospital.

POSTOPERATIVE HYPERCHOLESTEREMIA WITH NORMAL OR LOW METABOLISM

In chart 2 are shown findings in eighty-nine unselected postoperative cases with a cholesterol value of 200 mg. or more. Some of the patients with high cholesterol values later showed normal values without treat-

ment. To be noted in chart 2 is the higher incidence of clinical myxedema as higher cholesterol values are reached, as well as the better results obtained from administering desiccated thyroid. The metabolic rates vary considerably, and some are above the normal average; these discrepancies may be due to emotional disturbances which occur from time to time. Although they can hardly be considered true basal metabolic rates, it did not seem desirable to omit them from the chart.

SUCCESSIVE CHANGES IN THE BLOOD CHOLESTEROL IN THE DEVELOPMENT OF POSTOPERATIVE MYXEDEMA

As stated in part II of this study,^{18a} the blood cholesterol may be said to follow one of three courses after operation for hyperthyroidism. 1. It

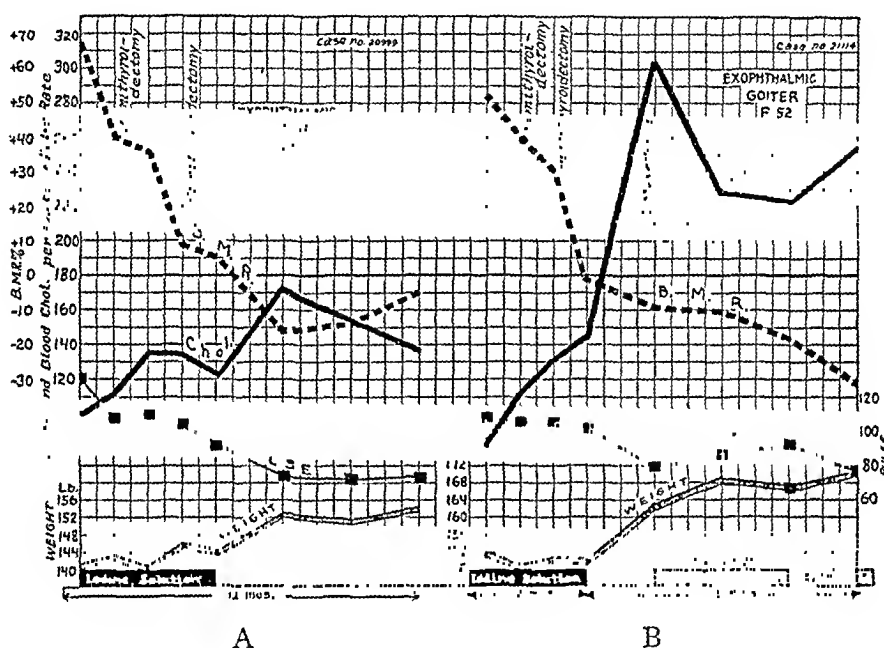


Chart 3.—*A*, data on a case of severe exophthalmic goiter; note the effect of a compound solution of iodine (represented by solid black) and two hemithyroidectomies. There was a postoperative low basal metabolic rate without hypercholesteremia. The basal metabolic rate returned to normal, and there was a slight drop in cholesterol at the end of nine months. *B*, the effect of a compound solution of iodine and two hemithyroidectomies in a case of severe exophthalmic goiter. There was postoperative hypercholesteremia without a low metabolic rate or clear-cut myxedema. Administration of desiccated thyroid lowered the cholesterol; the omission of thyroid for three months showed a rise in the cholesterol, an increase in weight, a drop in the basal metabolic rate and the pulse rate and a return of the symptoms. Administration of compound solution of iodine is indicated by solid black at the lower border of the chart.

18a. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease; II. Effect of Treatment, *Arch. Int. Med.* 52:86 (July) 1933.

may return to normal and remain within the normal range (chart 3*A*). 2. It may rise above normal with or without clinical myxedema and subsequently fall within the normal range without treatment (charts 4*A*, 4*B* and 5*B*). 3. It may rise above normal and remain there, usually with the development of myxedema, unless reduced by the administration of thyroid (charts 3*B*, 5*A* and 6*B* and *C*).

The effect of roentgen treatment over the thyroid is shown by the two cases illustrated in charts 6*A* and 7. In one case, roentgen therapy was given for a keloid scar six months after operation, by which time a temporary hypercholesteremia had subsided. Thereafter myxedema developed, and in view of the aforementioned events, it is reasonable

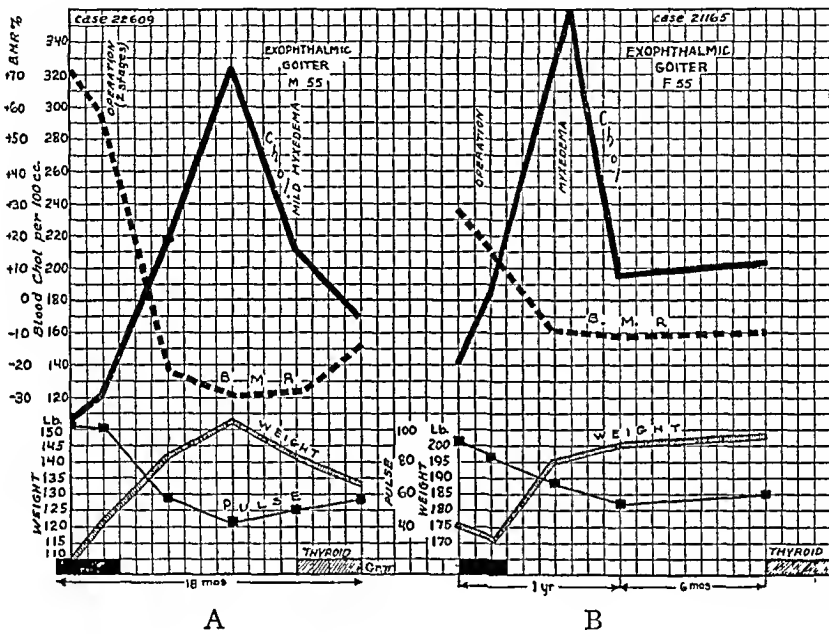


Chart 4.—*A*, the effect of a compound solution of iodine on severe exophthalmic goiter before the first operation. Two hemithyroidectomies resulted, in three months, in a low basal metabolic rate and a cholesterol level of 220 mg. For a while there were no symptoms; three months later there were hypercholesteremia, a further drop in the basal metabolic rate and in the pulse rate and an increase in weight; there were no complaints other than a dry skin and an excessive gain in weight. Thyroid therapy was prescribed. When thyroid was not taken there was a spontaneous drop in cholesterol and in weight; after the thyroid was taken, a rise in the basal metabolic rate and pulse rate and a further drop in cholesterol and weight occurred. *B*, the effect of subtotal thyroidectomy on moderate exophthalmic goiter: postoperative hypercholesteremia without marked hypometabolism, and definite clinical myxedema of mild degree. No treatment was given. There were a normal range of cholesterol and a normal basal metabolic rate at the end of a year and eighteen months, and suggestive evidence of slight myxedema but marked improvement in well-being. Thyroid therapy was prescribed as a trial, with some (?) improvement, as reported by letter. Solid black indicates administration of compound solution of iodine.

to assume that thyroid deficiency resulted from the effect of the roentgen rays on the thyroid remnant. In the second case (chart 7), hypercholesteremia with mild but transient myxedema was produced when roentgen rays and compound solution of iodine were used. A cholesterol level of 575 mg. was found in another patient who had received a long series of roentgen treatments following operation for what was thought to be exophthalmic goiter. As the symptoms did not improve with roentgen therapy, she was referred to the Lahey Clinic for further operation. The basal metabolic rate was reported elsewhere as always above $+20$. The patient continued to complain of palpitation and nervousness, although she felt cold and weak and presented a very dry skin. Thyroid was therefore tried for a period; this further increased

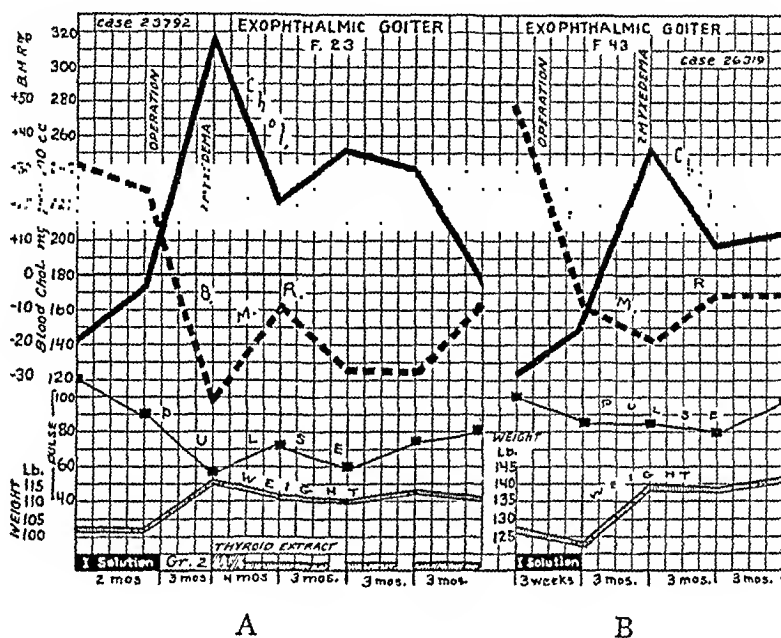


Chart 5.—*A*, effect of compound solution of iodine and operation on moderate exophthalmic goiter: postoperative hypercholesteremia, hypometabolism and borderline myxedema. The effect of thyroid therapy is shown. Omission of thyroid for several weeks caused a rise in cholesterol and a drop in the basal metabolic rate. The continuation of thyroid and the omission again before the last observation maintained the cholesterol and the basal metabolic rate at the same level as on the previous omission, although physical signs were not clearcut. The symptoms were those of thyroid deficiency, and they were relieved by the administration of thyroid. *B*, data on a case of moderate exophthalmic goiter, in which operation was followed by hypercholesteremia and hypometabolism of moderate degree without clearcut myxedema. The treatment was purposely withheld; there were a return to normal range and an improvement in symptoms. Compound solution of iodine is indicated by solid black.

the nervousness and palpitation. It was therefore discontinued. The sensitiveness to cold and the dryness of the skin disappeared. When the patient was seen nine months later, there was no evidence of thyroid deficiency, although the thyroid pills had been stopped eight months before. The blood cholesterol at that time was 238 mg. Apparently the

thyroid had been temporarily depressed as the result of roentgen treatment and then had recovered. Basal metabolic studies were not obtained in this case.

CHRONIC THYROIDITIS

In part I of this study it was shown that the average cholesterol value for patients with chronic thyroiditis was above the normal average. Patients with frank myxedema were not included in this group. Not every patient with chronic thyroiditis will show a cholesterol value above the average, because there are two other factors which influence the blood cholesterol in this disease: (1) The element of infection, if it has not passed the active stage, tends to lower the cholesterol; (2) it is

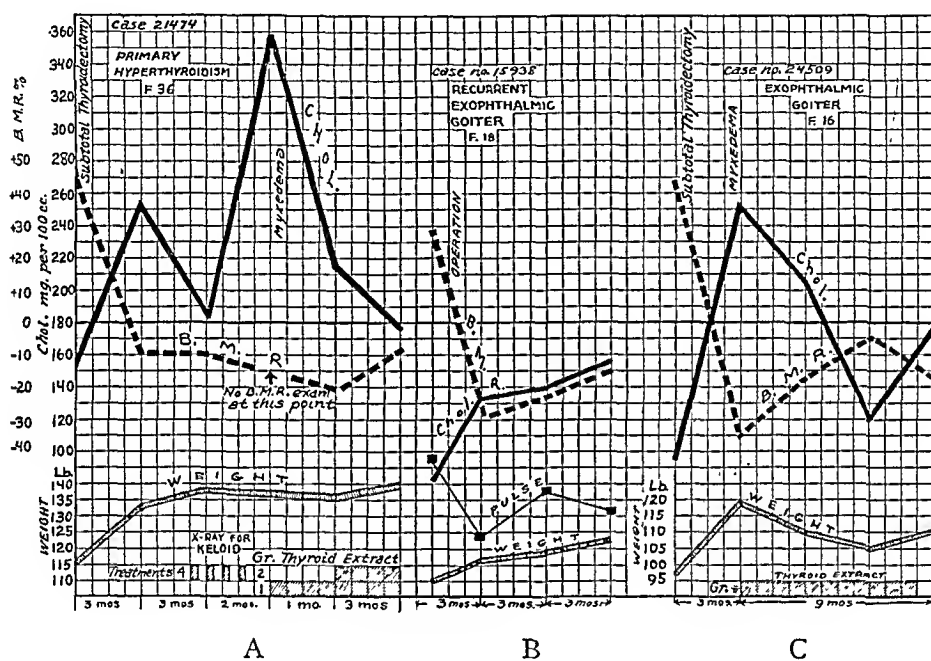


Chart 6.—*A*, exophthalmic goiter. Subtotal thyroidectomy resulted in temporary postoperative hypercholesteremia, and roentgen therapy for the keloid scar caused by the incision was followed by the development of myxedema. Treatment with desiccated thyroid was instituted. *B*, recurrent exophthalmic goiter. The thyroid remnants were excised. Postoperatively there were a low basal metabolic rate, headache and amenorrhea (menstruation had been scanty and irregular for years). Administration of desiccated thyroid afforded no improvement. There was a gradual return of the metabolism to normal without hypercholesteremia. *C*, exophthalmic goiter. Subtotal thyroidectomy was followed by myxedema, low metabolism and hypercholesteremia. Thyroid extract was administered for eight and one-half months; it was omitted for two weeks before the last observation.

not uncommon for a mild hyperthyroidism to be present in the early stage of the disease. Postoperative myxedema is probably more likely to occur in chronic thyroiditis if operation is performed than in ordinary exophthalmic goiter. In fact, simply removing the isthmus for relief

of tracheal pressure may be followed by myxedema. The development of hypercholesteremia after operation in a case of this type, without previous hyperthyroidism, clearly demonstrates that it is the result of thyroid deficiency and substantiates the contention that hypercholesteremia following subtotal thyroidectomy for toxic goiter is due to thyroid deficiency rather than to the previous presence of increased thyroid activity such as has been described following hyperthyroidism induced with thyroid extract.^{7b}

In one case of chronic thyroiditis which was seen since part I of this study was submitted, a cholesterol value of 680 mg. was found. Six months prior to admission, the patient had severe tonsillitis followed by soreness in the neck. Following this the patient became easily fatigued,

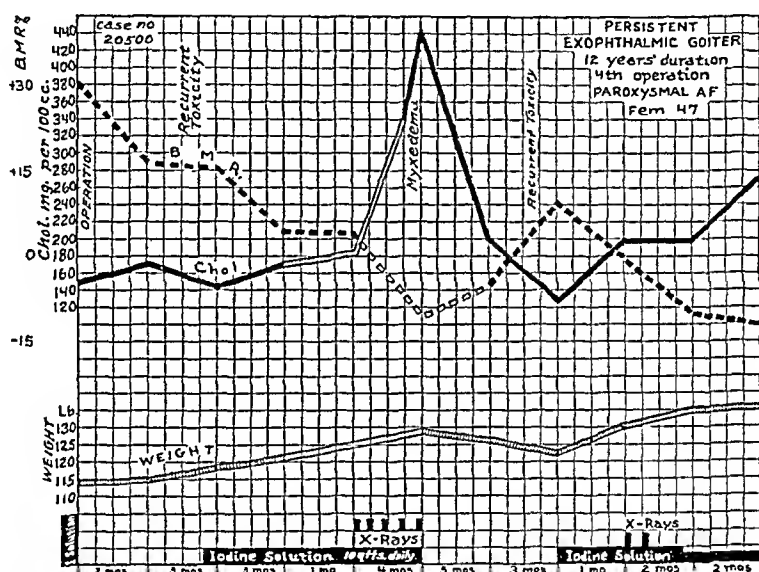


Chart 7.—Data on a case of persistent exophthalmic goiter of twelve years' duration at the time of the fourth operation; compound solution of iodine was not given for four months after the operation, at which time a recurrence took place and the solution was resumed. There were a drop in the basal metabolic rate and a rise in cholesterol; five roentgen treatments were given over the thyroid. Hypercholesteremia and mild myxedema (feeling of coldness, sleepiness and a dry skin) developed; toxicity recurred at the end of six months, with a drop in the cholesterol and a rise in the metabolic rate; administration of compound solution of iodine caused a drop in the basal metabolic rate and a rise in cholesterol; two more roentgen treatments caused a further drop in the basal metabolic rate but no change in the cholesterol. The patient is now well. The unshaded short lines in the chart indicate no observations; the lines are used merely to connect the preceding and the following observations. Solid black indicates compound solution of iodine.

gained weight and could carry on her work only with great effort. On examination, the thyroid was about three or four times its normal size and firm in consistency throughout. The appearance of the patient, the

character of the skin, and the complaints as related to myxedema were inconclusive. A diagnosis of myxedema could therefore not be definitely made. The first basal metabolic rate was plus one. This test could not be repeated at the time, so that it cannot be stated conclusively that this represented the true basal rate; yet there was no difficulty in taking the test, and the patient spent a quiet night in the hospital beforehand. However, as the likelihood of thyroid deficiency with chronic thyroiditis was known, she was given thyroid extract, 2 grains (0.13 Gm.), U. S. P., per day, before the report of the blood cholesterol was received. The results of treatment in her case have been so striking, and her appear-

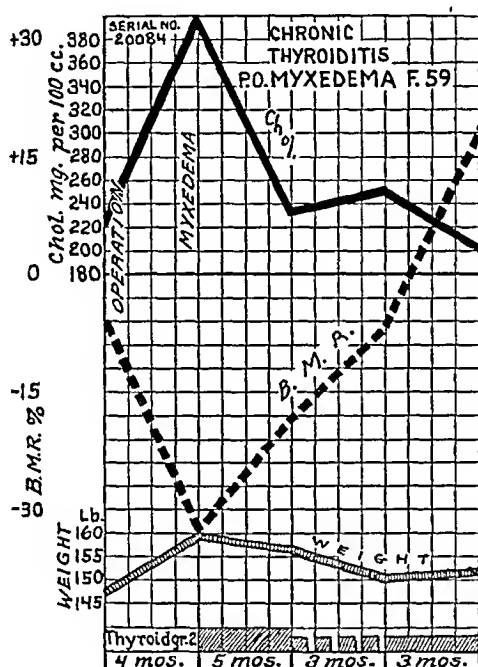


Chart 8.—Data on a case of chronic thyroiditis in which the cholesterol was above, and the basal metabolic rate below, the normal average. On the removal of the thyroid isthmus, myxedema developed. The effect of thyroid administration is shown. Irregular administration of thyroid resulted in a slight rise in cholesterol, with a return to the normal level when a smaller dose (1 grain [0.065 Gm.]) was given regularly. The cholesterol values in this case proved to be the most reliable laboratory guide in the treatment. The last metabolic rate particularly was the result of some emotional upset.

ance and behavior have changed so remarkably that the diagnosis of myxedema cannot be questioned.

Chart 8 shows observations on a patient with chronic thyroiditis who was operated on for relief of pressure. Only the thyroid isthmus was removed. In four months the patient returned with typical myxedema. Desiccated thyroid was then administered, with the usual relief. The cholesterol curve which displays a contour similar to that of the weight

curve is to be noted. The last basal metabolic rate is inconsistent with the cholesterol value and weight; it was probably caused by some emotional disturbance at the time of observation.

Of eight patients with chronic thyroiditis who were operated on and whose blood cholesterol was determined before operation, typical myxedema and hypercholesteremia of over 300 mg. developed in four. Of the remaining four patients, one showed no significant change in metabolic rate, cholesterol or physical condition (except a gain of 49 pounds [22.2 Kg.] in four months); another showed a lower metabolism and a slight rise in cholesterol but no obvious change in physical

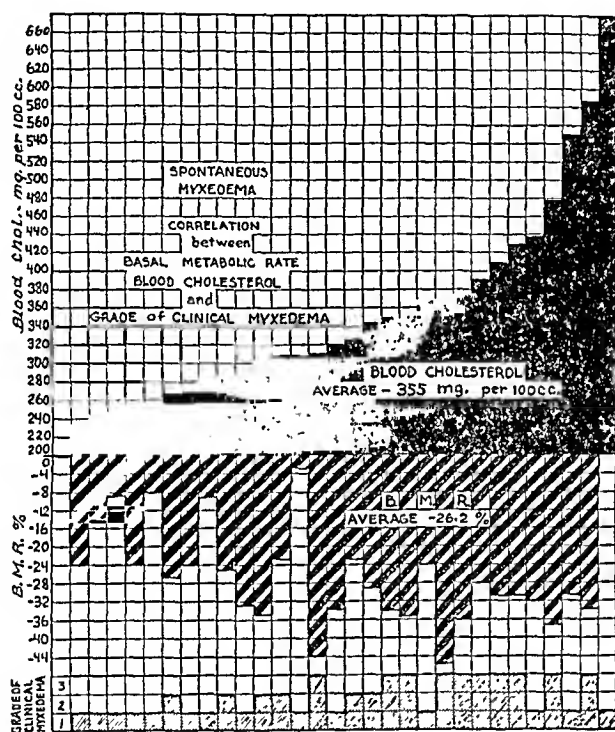


Chart 9.—The findings in patients with myxedema before treatment was started and an estimate of the degree of clinical myxedema. In a general way, the greater the cholesterol and the lower the metabolism, the greater is the degree of myxedema. In several cases, and especially the last case, the first estimate of the degree of myxedema was erroneous, as judged from observations following treatment.

condition; a third, who probably had mild hyperthyroidism, showed a rise of from 189 to 248 mg. and a drop in metabolism of from +15 to -13 per cent without physical change; the fourth was distinctly toxic and showed a rise in cholesterol of from 181 to 305 mg. with a drop in metabolism of from +35 to -3 per cent and a gain of 15 pounds (6.8 Kg.) in weight. Up to the time of writing there was no evidence of myxedema. In five other patients with chronic thyroiditis who were operated on and in whom myxedema developed afterward, the blood cholesterol values were all more than 300 mg. (Determination of the blood cholesterol was not made before operation in these cases.)

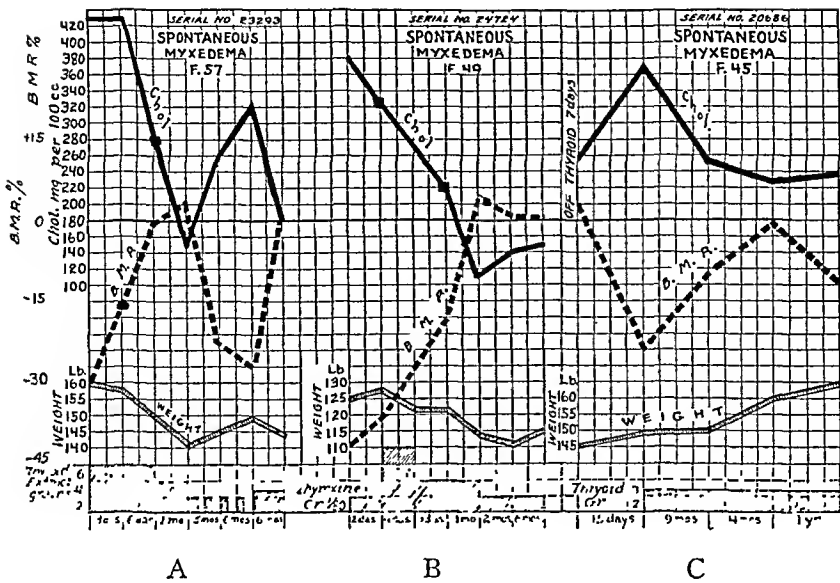


Chart 10.—*A*, myxedema of many years' duration. Thyroid was administered, 6 grains (0.4 Gm.) a day for nine days; then the patient was discharged on a dosage of 4 grains (0.26 Gm.) a day. Too rapid administration proved disagreeable to the patient. Although the dose was reduced to 2 grains (0.13 Gm.) a day at the end of the month, the patient took this irregularly until finally, with the gradual increase of the dose from 2 to 3 grains (0.13 to 0.2 Gm.) a day, the patient returned, relieved of myxedema and in good condition, except that angina pectoris was present on exertion. The dose was reduced. This case illustrates the reciprocal relationship between metabolism and cholesterol. The percentage of elevation of the cholesterol as compared to the lowering of the basal metabolic rate was approximately in the ratio of 5:1. *B*, myxedema. Illustrating the rapid fall (similar to that in *A*) of cholesterol during a period of days and a rise in the basal metabolic rate on administration of thyroid. At the end of one month the dose of 4 grains (0.26 Gm.) of thyroid proved too much, and the dose was reduced to 2 grains (0.13 Gm.) for two months. This proved to be the optimum dose and was, therefore, continued for six months. Note the gain in weight, although the basal metabolic rate and the cholesterol remained the same. The ratio in percentage between the height of the cholesterol before treatment and the depression of the basal metabolic rate was approximately 3:1. *C*, myxedema. The patient discontinued thyroid therapy seven days before coming under my observation. The basal metabolic rate and the cholesterol were within the normal range. Thyroid was further discontinued for fifteen days, with a short drop in the basal metabolic rate and a rise in cholesterol. Three grains (0.2 Gm.) of thyroid were then administered. The initial drop in weight was not recorded, as the patient left the hospital, but thereafter a gain in weight continued in spite of the improvement in the basal metabolic rate and the cholesterol. The ratio here between the height of the cholesterol and the lowering of the basal metabolic rate in per cent was approximately 4:1.

SPONTANEOUS MYXEDEMA

Thirty additional cases of spontaneous myxedema in which studies of the cholesterol were made have been observed. These are graphically shown in chart 9. Five of the patients had a metabolic rate between 0 and -12 per cent. I was able to repeat the tests in three instances, in two of which there was a 5 per cent decrease on the second day in the hospital and in another of which there was a 3 per cent decrease. It is possible that in these cases a lower rate could have been obtained, but since no difficulty was encountered by the patients in taking the test, it is only a possibility. Although it may be doubted that these are true basal rates, it is important to point out that such readings are obtained even under most favorable conditions and therefore may be misleading. It is interesting to note, how-

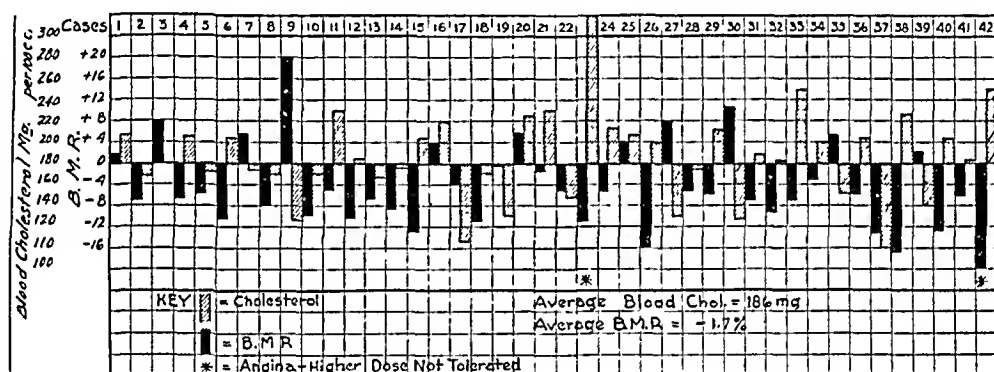


Chart 11.—The findings in forty-two cases of myxedema (operative and spontaneous) when optimum doses of desiccated thyroid or thyroxine were being administered. The value of the cholesterol or the basal metabolic rate is shown by polygons projected above or below the normal average base line. If the polygons for cholesterol were represented in percentage deviation from normal, they would be approximately twice their present size. It is to be noted, however, that the cholesterol of the majority is below 220 mg.

ever, that in one hundred and twenty cases of hypothyroidism, Rowe and Lawrence¹⁹ found a basal metabolic rate of -10 or less in every instance.

RESULTS OF TREATMENT AND THE BEHAVIOR OF THE BLOOD CHOLESTEROL IN SPONTANEOUS MYXEDEMA

In chart 10 is shown the course following treatment in three cases, in one of which thyroid was given and then taken irregularly, in another of which thyroid was omitted when the patient had been adequately treated, and then resumed and in a third of which thyroid was continued

19. Lawrence, C. H., and Rowe, A. W.: Studies on the Endocrine Gland: III. The Thyroid, *Endocrinology* **12**:377 (July-Aug.) 1928.

without interruption. The rapidity with which the metabolic rate and the cholesterol can be altered in a few days is to be noted also. (Rapid treatment, however, should be discouraged, for, although effects of thyroid may be noted more quickly, it is doubtful if time or added benefit is gained in the long run. Starting treatment on the average daily ration will produce the desired results without the disturbing symptoms occasionally seen when large doses are given.)

THE OPTIMUM RESULT IN RELATION TO THE BLOOD CHOLESTEROL AND BASAL METABOLIC RATE

In chart 11 are shown the cholesterol values in relation to the metabolic rate when the patient was considered to be on the proper ration of thyroid. Two cases depart considerably from the average; in these, angina developed on every attempt to increase the dose. The averages for the group show normal values.

CRETINISM

The blood cholesterol was studied in three cretins. One had been adequately treated, another had received inadequate treatment, and a third had been suspected of cretinism and had received small doses of thyroid, without benefit. The blood cholesterol was over 300 mg. in all three patients when they were not receiving thyroid. In the third case, the determination of the blood cholesterol was of great value in diag-

TABLE 2.—*Effect of Thyroid on Cholesterol in a Cretin*

Age	Cholesterol, Mg. per 100 Cc.	Weight, Pounds	Thyroid, Grains	Time, Weeks	Result
21 months	370	28.0	1		
	130	23.5	1	3	Improved
	121	23.5	1	6	Improved

nosis. The child had been observed in one hospital and discharged with the diagnosis of questionable cretinism. Because inadequate doses of thyroid had not produced beneficial results, the child was taken to several clinics, at which it was stated positively that the child was not a cretin. On first examination, the child displayed rather coarse features, but the skin was very soft, and the hair was fine and not brittle. The blood cholesterol was found to be 370 mg., and thyroid was tried in larger doses, following which remarkable clinical improvement occurred.

HYPERCHOLESTEREMIA IN DIAGNOSIS

It is obvious from what has been written in this report that when hypercholesteremia is found, except, of course, in diabetes mellitus, nephrosis and obstruction of the common duct, it is considered as possibly of thyroid origin. In patients with mental disorders, hypercho-

lesteremia has been reported by several observers.²⁰ Duncan^{14g} tried thyroid extract in one patient with hypercholesteremia and dementia praecox. He described the patient as subthyroidic, thus inferring that typical myxedema was not present. The usual fall in cholesterol took place, and the patient became normal. When the administration of thyroid ceased, all of the symptoms returned, and hypercholesteremia again took place. Another of Duncan's patients with hypercholesteremia of less extent showed no improvement. In one case which I observed, the chief complaint was aural hallucinations. Examination suggested mild myxedema. The basal metabolic rate was determined, which was —22 per cent. In this patient, who was first seen over four years ago, the cholesterol value was not determined until recently, when the patient stopped taking thyroid for several weeks, at which time hallucinations again returned and hypercholesteremia was present. Administration of thyroxine was resumed, and a return to normal took place within a few days. Experience with two other patients suffering from mental depression and hypercholesteremia without evidence of myxedema, and with patients who have definite myxedema with mental disturbances of various types has suggested that a therapeutic trial is indicated in any mental case with hypercholesteremia, regardless of the metabolic rate, and that hypercholesteremia may be a more rational indication of thyroid deficiency in certain instances than a low metabolic rate per se.

The application of such a therapeutic trial of thyroid to other conditions is worthy of consideration. In the case cited earlier, in which chronic thyroiditis and a cholesterol value of 680 mg. were present, five physicians saw the patient, but the possibility of myxedema did not occur to them. Obesity and fatigue from overwork had been the usual diagnoses. Furthermore, the basal metabolic rate obtained was normal. Here, then, was a case of obesity of thyroid origin in which the diagnosis would not have been made in five of six instances without the strong possibility suggested by the hypercholesteremia and the presence of a thyroid gland characteristic of chronic thyroiditis.

Another patient recently came to the clinic with the complaint of goiter and renal disease. Moderate hypertension was present, the non-protein nitrogen was above normal, albuminuria was marked, and the specific gravity of the urine was fixed. The basal metabolic rate was normal on three occasions. The appearance of the patient was consistent with chronic nephritis or mild myxedema. There was no pitting edema present. The blood cholesterol was over 400 mg. The serum protein was normal. On receiving thyroid extract the patient showed a remarkable improvement; the nodules in the thyroid disappeared, and the nonprotein nitrogen became lower. (This case will be reported in detail at a later date.) The condition could easily have passed unnoticed, with only

20. Schube,^{14b} Duncan^{14c} and Grabfield.^{14e}

a diagnosis of chronic nephritis and without the great benefit resulting from the knowledge that myxedema was the chief cause of her complaints.

Pernicious anemia may occur in patients with myxedema.²¹ One of the patients included in this study complained of inability to lose weight and difficulty in walking. She had taken inadequate amounts of liver on prescription before admission. The appearance of the patient did not suggest myxedema. The skin showed a yellowish tint and the cheeks were pink. The skin was soft and smooth, and the patient perspired and had no sensation of coldness. The last two points I wish to emphasize for they were affirmed again and again by the patient and her sister. The texture of the skin was striking in its fineness. There was no free hydrochloric acid found in an aspirated test meal. The red cell count and the hemoglobin were subnormal but, it was felt, not diagnostic because of previous liver therapy. Vibratory sense as indicated by the tuning fork was diminished in both legs. The reflexes were normal. Believing that further intensive liver therapy was indicated, liver extract was given intramuscularly three times a week, and approximately $\frac{1}{2}$ pound (0.2 Kg.) of liver was eaten daily by the patient. At the end of one month, there was no change; the condition of the blood remained stationary. Only one clue to the possibility of myxedema was furnished by the patient's sister, after reflection over a question put to her, namely, that the patient talked a little more slowly during the past few years than previously. A specimen of blood was taken to determine the cholesterol value, which was 535 mg. The basal metabolic rate was then found to be — 30 per cent; had this not been low, I feel sure that the true diagnosis would have been passed by. Desiccated thyroid has completely changed the patient's condition, and her true normal condition can now be seen in striking contrast to her previous state. Apparently the condition had come on so gradually that the sister with whom she lived was unaware of it.

In seventeen cases in which the blood cholesterol was over 250 mg. classification has been difficult. In seven of these cases found after operation for toxic goiter, three patients have not been able to return for further study. The other four have been observed over periods of one or two years, and hypercholesteremia persists with normal basal metabolic rates (above — 10 per cent). No evidence of myxedema was found in three patients, and only suggestive evidence in one. All of the patients feel well. Two are excessively overweight and are taking thyroid, without toxic symptoms, but with loss of weight and reduction in the blood cholesterol (table 3).

21. Means, J. H.; Lerman, J., and Castle, W. R.: The Coexistence of Myxedema and Pernicious Anaemia, *New England J. Med.* **204**:246 (Feb. 5) 1930.

TABLE 3.—*Effect of Administration of Thyroid on Postoperative Hypercholesteremia Without Evident Myxedema*

Date	Basal Metabolic Rate, per Cent	Cholesterol, Mg. per 100 Cc.	Pulse Rate	Weight, Pounds	Desiccated Thyroid, Grains per Day	Comment
Woman, Aged 54 (19312): Toxic Adenomatous Goiter						
12/ 5/30	+30	...	100	187	..	Subtotal thyroidectomy
9/22/31	— 4	307	80	202	..	No complaints
12/17/31	+ 3	312	80	219		
5/ 2/32	+ 5	312	80	209	..	Weight reduced by diet
1/ 4/33	308	90	219½	2	Thyroid started; no diet
1/18/33	268	84	210	3	Thyroid increased
5/13/33	+11	245	92	202	3	Feels better; loss of 17½ pounds with thyroid therapy
Woman, Age 21 (18954): Exophthalmic Goiter						
11/ 6/30	+85	...	120	126	..	Very toxic; subtotal thyroidectomy
11/21/31	+ 7	312	80	150	..	Went through pregnancy
12/15/31	397	..	157	.	No complaints; periods irregular
11/21/32	+12	329	98	163	..	No complaints
1/ 4/33	242	90	163	2	Thyroid started
2/ 4/33	297	88	157	3	Thyroid increased to 3 grains but stopped for a while, then resumed; hence gain in weight on 4/25/33
4/25/33	258	100	164	4	Periods regular and increased in amount; feels "peppier"; thyroid increased
5/15/33	+45	...	128	157	4	Thyroid reduced

TABLE 4.—*Results of Thyroid Therapy in Seven Patients not Operated on or Showing no Changes in the Thyroid*

Number	Clinical Impression	Complaint or Other Diagnosis	Basal Metabolic Rate	Cholesterol	Dose, Grains	Results
22562	Mild myxedema suspected	Fibroid uterus; fatigue; obesity	—18	280 (225)*	2	Excellent result
26671	Accidental finding	Constipation; "bloat"; obesity; hypertension	—15	272	2	Anginal symptoms developed; thyroid therapy stopped (report by mail)
23007	Accidental finding	Depression; obesity	— 9	260 (226)*	2	Not depressed when taking thyroid
27618	Mild myxedema suspected	Angina pectoris; obesity	294	1	Symptoms worse on 1 grain a day (stopped)
27262	Mild myxedema suspected	Peripheral vascular disease; anemia; fatigue	— 8	342 (216)*	2	No definite improvement
21821	Said to have myxedema	Constipation; thyroid stopped 2 weeks before	—15	284	0	No thyroid taken for 1 year; feels fine (report by mail)
31081	Obesity	Obesity; coldness	— 3	272	2	Excellent result

* This estimate was made after administration of thyroid.

Two other cases in this group of seventeen cases in which the blood cholesterol was over 250 mg. were found following removal of a non-toxic goiter. There were no complaints and no evidence of thyroid deficiency. In another case the patient showed a cholesterol value of 305 mg. before operation and of 336 mg. three months after operation. The patient stated that she had always felt cold and tired. Her skin was dry but otherwise displayed no evidence of thyroid deficiency. Thyroid was prescribed, and the patient wrote that although she felt much better when taking it, she became depressed and discontinued it. The remaining seven patients showed no changes in the thyroid and had not been operated on. They are listed with the results of thyroid therapy in table 4.

It is well to point out that this list would have been larger if I had included in it cases in which the initial diagnosis was distinctly in question, yet which were undoubtedly cases of myxedema, as proved by the striking results of the administration of thyroid.

Hypothyroidism without myxedema, amyxedemic thyroid failure and primary thyroid failure are terms which have been used to express in certain cases the combination of various symptoms and hypometabolism. Undoubtedly some of these are cases of thyroid deficiency, but it is also possible that some are not. It seems reasonable to conclude, on the basis of these studies, that thyroid failure always gives rise to myxedema and a rise in the cholesterol, but that the myxedema may be unrecognized because of the lack of characteristic physical findings, and can therefore rightly be termed imperceptible myxedema. Lawrence and Rowe¹⁹ demonstrated an initial loss of weight in the case which they described as one of amyxedemic thyroid failure with a subsequent gain in weight. This is a common observation in clinical myxedema. This initial loss of weight in the atypical case, it would seem, is due to the loss of water from concealed myxedema. An analogy may be said to occur in congestive heart failure when occasionally no perceptible edema can be demonstrated, yet in which a masked diuresis can be produced by a diuretic. An occasional case with obvious myxedema in which the cholesterol may be considered within the upper limits of normal may be found, yet this does not vitiate the statement that hypercholesteremia is characteristic of thyroid deficiency, because for a certain person the high normal value may well represent an increase of 100 per cent over his normal level.

CONCLUSIONS

1. Postoperative myxedema is accompanied by hypercholesteremia.
2. Subtotal thyroidectomy may be followed by hypercholesteremia without clinical myxedema. This is interpreted as a transient thyroid deficiency.

3. Subtotal thyroidectomy may be followed by low metabolic rates, without hypercholesteremia. In these cases myxedema is seldom found.

4. Roentgen therapy can produce transient hypercholesteremia with or without clinical myxedema.

5. Removal of part of a thyroid gland affected by chronic thyroiditis may be followed by hypercholesteremia and myxedema.

6. Thyroid deficiency produces myxedema and hypercholesteremia, but at times myxedema may be clinically imperceptible.

7. Hypercholesteremia, when not explainable on any other basis, may be considered as possibly of thyroid origin, and is a rational indication for thyroid administration.

8. The finding of hypercholesteremia, in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low metabolic rate. Finding both renders the possibility of thyroid deficiency extremely likely.

9. The relationship between the blood cholesterol and the basal metabolism is usually reciprocal when they undergo change as the result of variations in the activity of the thyroid gland or thyroid substance in the body.

10. The blood cholesterol provides another variable which may be used as a guide in the treatment of thyroid disease.

Miss Bessie A. White, of the New England Baptist Hospital, collected many of the specimens of blood, and Miss Hazel M. Hunt, director of the chemical laboratories of the New England Deaconess Hospital, supervised the many analyses of the blood.

CEREBROSPINAL FLUID PRESSURE AND VENOUS PRESSURE IN CARDIAC FAILURE

AND THE EFFECT OF SPINAL DRAINAGE IN THE TREATMENT OF CARDIAC DECOMPENSATION

WILLIAM GROCE HARRISON, JR., M.D.

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That the venous pressure is elevated in persons with cardiac failure has been shown by a number of observers. Eyster and Middleton¹ and also Clark² clearly demonstrated by the indirect method of measurement that the venous pressure is an accurate guide to the course and prognosis in cardiac disease. A rising or persistently elevated venous pressure was found to offer a grave prognosis, while a falling venous pressure was observed to run parallel to the degree of improvement of the clinical condition of the patient. In studying venous pressure in cardiac failure and numerous other conditions, Harrison,³ using the direct method, reached the same conclusion. He found that the so-called average normal pressure determined by this method was about the same as that reported for the indirect method used by Eyster.^{4a}

It is well known that when the Queckenstedt test is performed pressure on the internal jugular vein is immediately followed by a rise in the cerebrospinal fluid pressure, provided there is no block. It occurred to me that perhaps persons with cardiac decompensation who show an elevation of venous pressure might likewise show an increase in cerebrospinal fluid pressure. Accordingly lumbar puncture was performed on a patient with marked congestive heart failure, and the pressure of the fluid was found to be greatly increased. Further studies were therefore carried out.

From the Department of Internal Medicine, Emory University School of Medicine, and Grady Memorial Hospital (colored unit).

1. Eyster, J. A. E., and Middleton, W. S.: Clinical Studies on Venous Pressure, *Arch. Int. Med.* **34**:228 (May) 1924.

2. Clark, A.: A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, *Arch. Int. Med.* **16**:587 (Oct.) 1915.

3. Harrison, W. G., Jr.: Clinical Studies in Venous Pressure, to be published.

4. Eyster, J. A. E.: (a) Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929; (b) Clinical and Experimental Observations upon Cheyne-Stokes' Respirations, *J. Exper. Med.* **8**:565, 1906.

SPINAL FLUID AND VENOUS PRESSURES IN CONDITIONS OTHER THAN
CONGESTIVE HEART FAILURE

The spinal fluid and venous pressures were studied in ten persons, none of whom had any evidence of congestive heart failure. In all instances the patients were resting quietly in bed. The spinal fluid pressure was recorded by means of the Ayer water manometer when lumbar puncture was performed, with the patient lying on his side in the prone position with his head on two flat pillows. The venous pressure in millimeters of water was determined by the direct method of Moritz and Tabora,⁵ the patient lying flat on his back in the prone position with his head on two pillows. In determining the venous pressure care was exercised to make certain that the zero reading of the water

TABLE 1.—*Spinal Fluid Pressure and Venous Pressure in Ten Control Patients Having No Evidence of Congestive Heart Failure*

Patient	Condition	Spinal Fluid Pressure, Mm. of Water	Venous Pressure, Mm. of Water	Ratio
1. E. R.	Neurosyphilis	105.0	70.0	1.5
2. F. B.	Acute gastritis	80.0	65.0	1.2
3. T. T.	Arsphenamine hepatitis	110.0	60.0	1.8
4. C. C.	Fibrinous pleurisy	150.0	75.0	2.0
5. O. L.	Chronic nephritis	150.0	75.0	2.0
6. O. H.	Duodenal ulcer	100.0	75.0	1.3
7. H. H.	Chronic lymphatic leukemia.....	90.0	45.0	2.0
8. W. M.	Osteomyelitis	80.0	40.0	2.0
9. M. B.	Millary tuberculosis	110.0	65.0	1.6
10. A. N.	Hypertension	90.0	75.0	1.6
	Average	106.5	64.5	1.6

manometer, the vein and the right auricle were all at the same level. At least three readings were taken each time. Most of the observations were made in the afternoon. The venous pressure was usually determined first, and this was followed immediately by the spinal fluid pressure readings.

In all instances the spinal fluid pressure and the venous pressure were within the normal limits (table 1). It was found that there was a definite ratio between the spinal fluid pressure and venous pressure. Although this varied from 1:2 to 2:0, it was fairly constant and averaged 1.6. Undoubtedly, if a larger series of cases had been studied, this ratio would have been lower in some cases and higher in others, but in general this may be considered as the average normal ratio.

5. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exacter zu bestimmen, *Deutsches Arch. f. klin. Med.* 98: 475, 1910.

SPINAL FLUID AND VENOUS PRESSURES IN CONGESTIVE
HEART FAILURE

The spinal fluid pressure and venous pressure were next similarly studied in a group of ten patients with congestive heart failure, all of whom had either syphilitic aortic insufficiency or hypertensive heart disease (table 2). It was found that all the patients with increased venous pressure had an increase in spinal fluid pressure. In those who showed a marked increase in venous pressure the spinal fluid pressure was also greatly increased. The higher the venous pressure the higher was the spinal fluid pressure observed. The ratio between the spinal fluid pressure and venous pressure ranged from 1:4 to 1:8, and the average was 1:6. This is the same average ratio reported in the

TABLE 2.—*Spinal Fluid Pressure and Venous Pressure in Ten Patients with Congestive Heart Failure*

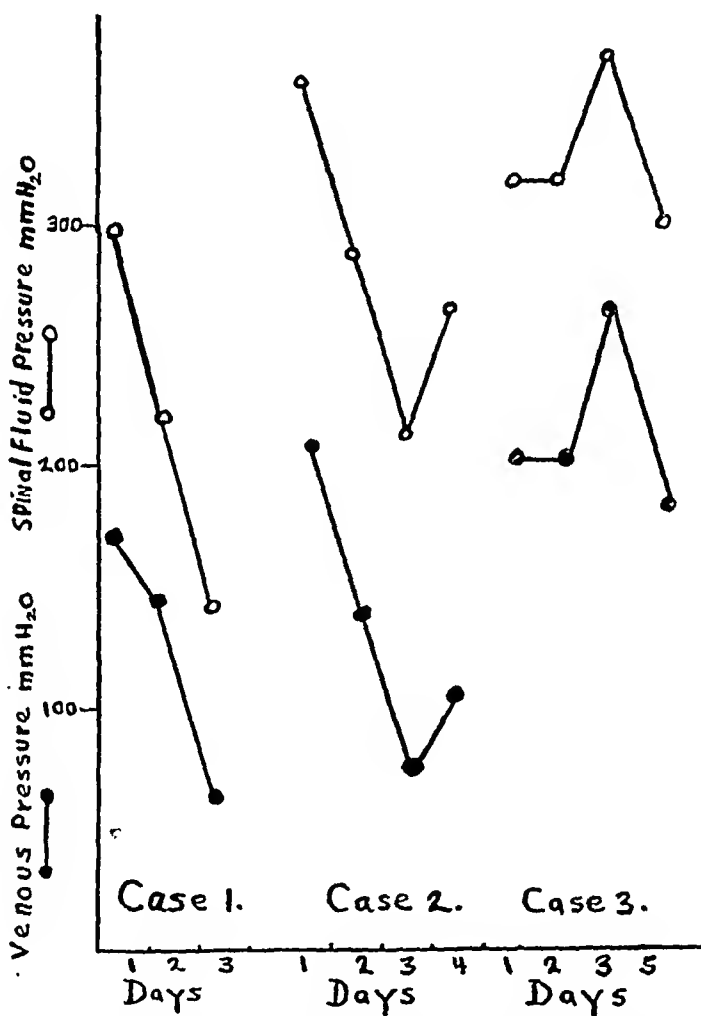
Patient	Condition	Spinal Fluid Pressure, Mm. of Water	Venous Pressure, Mm. of Water	Ratio
1. R. S.	Hypertensive heart disease.....	300.0	210.0	1.4
2. T. W.	Hypertensive heart disease.....	420.0	275.0	1.5
3. J. D.	Hypertensive heart disease.....	520.0	305.0	1.7
4. C. J.	Hypertensive heart disease.....	380.0	255.0	1.4
5. C. P.	Syphilitic aortic insufficiency.....	465.0	295.0	1.5
6. J. H.	Syphilitic aortic insufficiency.....	365.0	210.0	1.7
7. W. A.	Hypertensive heart disease.....	415.0	225.0	1.8
8. W. J.	Hypertensive heart disease.....	475.0	270.0	1.7
9. E. R.	Hypertensive heart disease.....	455.0	270.0	1.6
10. D. H.	Syphilitic aortic insufficiency.....	360.0	190.0	1.8
Average		415.5	250.5	1.6

control group (table 1), and it can be seen that in general this ratio tends to remain about the same. The average venous pressure in the group of patients with cardiac failure was 250.5, as compared with 64.5 in the control group, and the average spinal fluid pressure in the group with cardiac disease was 415.5, as compared with 106.5 in the control group. The spinal fluid pressure and venous pressure in the group with cardiac failure were nearly four times as great as in the control group. Thus, the cerebrospinal fluid pressure is markedly increased in patients with congestive heart failure.

EFFECT OF CLINICAL IMPROVEMENT ON THE SPINAL FLUID
AND VENOUS PRESSURES

The next series of observations consisted in following the changes in cerebrospinal fluid pressure and venous pressure as the patient with cardiac failure experienced clinical improvement under treatment (chart,

cases 1, 2 and 3). It can be seen that the changes in the spinal fluid pressure ran parallel to the changes in the venous pressure. When the venous pressure fell the spinal fluid pressure likewise fell. When the venous pressure rose the spinal fluid pressure rose. In case 1, in which the condition was syphilitic aortic insufficiency, both pressures fell to normal as the patient improved. In case 2, in which the condition was also syphilitic aortic insufficiency, both pressures fell nearly to normal



This chart shows the effect of clinical improvement on the spinal fluid pressure and venous pressure. Note the parallel course of the two pressures in three patients with congestive heart failure.

but later rose slightly. At this point the patient left the hospital, and no more observations were made on her. In case 3, in which the condition was hypertensive heart disease, there was also a parallel rise and fall of the two pressures in a patient who at first did not respond well to treatment. These three cases show that, except for slight variations, the spinal fluid pressure runs closely parallel to the venous pressure as the patient with congestive heart failure regains compensation.

EFFECT OF SPINAL DRAINAGE ON DYSPNEA AND VENOUS PRESSURE
IN CONGESTIVE HEART FAILURE

Various drugs have been used to lower the venous pressure,⁶ but the results have not been very satisfactory. The striking effect of venesection in lowering the venous pressure in patients with cardiac failure has been repeatedly demonstrated, and it occurred to me that since the spinal fluid pressure was markedly increased in these patients spinal drainage might prove of some benefit. In thirteen instances, therefore, patients who had either syphilitic aortic insufficiency or hypertensive heart disease were subjected to spinal drainage, and the effect on dyspnea, as stated by the patient, and on the venous pressure was

TABLE 3.—*Effect of Spinal Drainage on the Spinal Fluid and Venous Pressures in Thirteen Patients with Congestive Heart Failure*

Patient	Condition	Amount of Spinal Fluid Removed, Cc.	Spinal Fluid Pressure, Mm. of Water		Venous Pressure, Mm. of Water	
			Before Removal	After Removal	Before Removal	After Removal
Cases in Which a Fall in Venous Pressure Occurred						
1. T. W.	Hypertensive heart disease.....	35	420.0	110.0	275.0	200.0
2. C. W.	Syphilitic aortic insufficiency....	20	375.0	150.0	285.0	260.0
3. J. H.	Syphilitic aortic insufficiency....	25	365.0	95.0	210.0	175.0
4. W. A.	Hypertensive heart disease.....	20	375.0	150.0	265.0	245.0
5. C. W.	Syphilitic aortic insufficiency....	20	250.0	150.0	130.0	100.0
6. W. A.	Hypertensive heart disease.....	20	320.0	120.0	210.0	165.0
7. W. B.	Syphilitic aortic insufficiency....	30	370.0	120.0	165.0	125.0
8. R. S.	Hypertensive heart disease.....	30	300.0	100.0	210.0	155.0
	Average.....	25	346.8	124.3	218.7	178.1
	Average fall in venous pressure	40.6
Cases in Which No Fall in Venous Pressure Occurred						
9. J. C.	Hypertensive heart disease.....	25	350	125	145	185
10. J. D.	Hypertensive heart disease.....	65	520	170	305	390
11. W. A.	Hypertensive heart disease.....	20	300	90	185	185
12. D. H.	Syphilitic aortic insufficiency....	20	360	150	190	190
13. R. S.	Hypertensive heart disease.....	40	290	20	120	120

studied. In one patient, W. A., drainage was carried out three different times, and the readings were listed separately in table 3. In another patient, R. S., drainage was carried out twice, and the readings were listed separately. The venous pressure was recorded in the manner previously stated immediately before and after drainage. The amount of spinal fluid removed varied (table 3).

In eight instances the venous pressure fell following spinal drainage. The fall was marked in some cases; in others it was not so pronounced. In none of the cases did the venous pressure fall as much as the spinal fluid pressure. At this point, therefore, the ratio between the spinal fluid pressure and the venous pressure was obviously not the same as before. The average fall in venous pressure in the eight instances was

6. Capps, J. A., and Matthews, S. A.: Venous Blood Pressure as Influenced by the Drugs Employed in Cardiovascular Therapy, J. A. M. A. **61**:388 (Aug. 9) 1913.

40.6 mm. of water. In two cases the venous pressure rose instead of fell. In three cases there was no change in the venous pressure. Most of the patients stated, however, that they were able to breathe better following spinal drainage. This seemed to be true also for some of those who had experienced no fall in venous pressure. Many of the patients were able to breathe with nearly as much comfort lying down as they previously had done sitting up. In the majority of the cases this effect appeared to be a temporary improvement.

EFFECT OF POSTURE ON THE VENOUS, SPINAL FLUID AND CISTERNAL PRESSURES

The improvement of the patients with cardiac disease after spinal drainage suggested further observations that might help to explain why patients with this disease breathe better in the sitting than in the prone position. It is well known that in normal persons the lumbar spinal fluid pressure is much greater in the sitting position than in the prone position. It seemed to me that the cisternal pressure should be lower in this position. Indeed, this pressure has been reported to be below zero in the sitting position in the normal person.⁷ The observations of Weed⁸ on animals showed definitely this difference in pressure in the two positions. On the other hand, I know of no observations on the cisternal pressure in congestive heart failure. While studying the spinal fluid in a patient with syphilis and while attempting to give a patient with cardiac failure some relief by spinal drainage, an opportunity was offered to measure the cisternal pressure in the two patients in the sitting and prone positions.

The venous pressure, lumbar spinal fluid pressure and cisternal pressure in the sitting position were studied in the patient with syphilis. This subject was used as the normal or control. He was then placed in the prone position on his side, and the observations were repeated. The venous pressure was recorded in the prone position with the patient on his back, as was previously stated. A specially constructed U manometer filled with physiologic solution of sodium chloride was used to record the cisternal pressure. The same procedure was then carried out on a patient with hypertensive heart disease and congestive failure. Observations were obtained on only one control patient and one patient with cardiac disease. Weed, Flexner and Clark⁹ have shown that the

7. Ayer, J. B., in *The Human Cerebrospinal Fluid. An Investigation of the Most Recent Advances, as Reported by the Association for Research in Nervous and Mental Disease*, New York, Paul B. Hoeber, Inc., 1926, p. 159.

8. Weed, L. H.: *Positional Adjustments of the Pressure of the Cerebrospinal Fluid*, *Physiol. Rev.* **13**:80, 1933.

9. Weed, L. H.; Flexner, L. B., and Clark, J. B.: *The Effect of Dislocation of Cerebrospinal Fluid upon Its Pressure*, *Am. J. Physiol.* **100**:246, 1932.

fall in cerebrospinal fluid pressure is proportional to the amount of fluid removed. This source of error, however, is small in these determinations, and for purposes of comparison it may be considered negligible, since it is the difference in the pressure readings in the two positions which is of special concern. Table 4 shows the results of the readings.

The venous pressure and lumbar spinal fluid pressure in both the control patient and the patient with cardiac disease were much greater in the sitting than in the prone position. The cisternal pressure, on the other hand, was much lower in each person in the sitting than in the prone position. In the patient with cardiac failure, however, the cisternal pressure was higher in the sitting position than in the control patient, and the difference in the cisternal pressure in the two positions was greater in the patient with cardiac disease than in the control. Although the difference between the cisternal pressure in the two

TABLE 4.—*Differences in the Venous, Spinal Fluid and Cisternal Pressures in One Control Patient and One Patient with Congestive Heart Failure in the Prone and Sitting Positions*

	Control Patient			Patient with Cardiac Failure		
	Prone Position	Sitting Position	Difference	Prone Position	Sitting Position	Difference
Venous pressure, mm. of water.....	50	70	20	310	355	45
Spinal fluid pressure, mm. of water..	125	430	305	400	680	280
Cisternal pressure, mm. of water....	102	15	87	355	100	255

positions was considerable in the control patient, in the patient with cardiac disease this difference was enormous—255 mm. of water. Thus, the cisternal pressure and consequently the pressure in the region of the medulla are markedly decreased when the patient changes from the prone to the sitting position, and this is more pronounced in the patient with cardiac failure than in the normal person. This observation suggests one reason why spinal drainage helps patients with congestive heart failure. It seems that drainage is partly equivalent to changing to a sitting position. It also suggests one important reason why patients with this condition breathe better in the sitting than in the prone position and hence furnishes considerable information on orthopnea.

COMMENT

The close relationship that exists between spinal fluid pressure and cerebral venous pressure has been definitely established.¹⁰ According

10. Hill: *Physiology and Pathology of the Cerebral Circulation*, London, J. & A. Churchill, 1896.

to Weed and Hughson,¹¹ alterations in the intracranial venous pressure effect changes in the pressure of the cerebrospinal fluid in the same direction but not to the same extent. Curiously enough, the spinal fluid pressure has not been thoroughly investigated in heart failure. In spinal drainage in a patient with cardiac disease one should guard against removing the spinal fluid too rapidly or taking out too much at once from a very ill patient with a markedly elevated venous pressure. Some of these patients complain of headache after drainage; hence, caution is advised in using this method of treatment.

A number of facts must yet be learned about spinal drainage in heart failure. In the first place, if a patient experiences improvement one should know how long this improvement will last. The effect usually appears to be temporary. One should know also how much fluid to remove. Unquestionably these factors vary with the clinical condition of the patient. The mild cases will not need drainage. The effect of hypertonic solutions, such as dextrose and magnesium sulphate, should be studied and may prove to be of value. The mechanism of clinical improvement and fall in venous pressure following spinal drainage in some of these patients has yet to be investigated, and studies are now being carried out along these lines. Before this method of treatment can be of great value therapeutically, the study of a larger series of cases is advisable.

In studying the changes in pressure observed in the sitting and prone positions in patients with cardiac disease, one has to consider the much discussed cause of orthopnea. That the vital capacity is increased in the sitting position, as compared with the prone position, has been definitely shown to be true.¹² Undoubtedly this is one of the major causes of orthopnea. Ernstene and Blumgart¹³ thought that orthopnea could be explained largely by the increased blood supply to the respiratory center as a result of the lowering of cerebral venous pressure when the patient assumed the erect position. The observations here reported tend to show that one reason why patients with cardiac disease breathe better in the sitting than in the prone position is that there is marked decrease in cisternal pressure and hence decrease in pressure on the medulla. Whether this is due to a direct effect of the pressure of the fluid, to an accompanying change in cerebral venous pressure or to some

11. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by the Intravenous Injection of Solutions of Various Concentrations, *Am. J. Physiol.* **58**:101, 1921.

12. Christie, C. D., and Beams, A. J.: Orthopnea, *Arch. Int. Med.* **31**:85 (Jan.) 1923.

13. Ernstene, A. C., and Blumgart, H. L.: Orthopnea: Its Relation to the Increased Venous Pressure of Myocardial Failure, *Arch. Int. Med.* **45**:593 (April) 1930.

indirect effect has yet to be ascertained. Certainly it appears that, in addition to the increased vital capacity, the decreased cisternal pressure is an important factor in producing the relief from dyspnea obtained in the sitting position. The studies here reported likewise explain Ern-stene and Blumgart's observations that, although the vital capacity of the patient with cardiac disease is not changed by flexion of the head, patients with this condition breathe better in this position than in the absolute prone position.

Eyster ^{4b} has shown that an increase in intracranial pressure will produce Cheyne-Stokes' breathing if waves of blood pressure are called forth to such an extent that the intracranial pressure alternately rises and falls above the level of arterial pressure. He thought that this might explain the cause of Cheyne-Stokes' respiration in some clinical conditions in which there is increased intracranial pressure, but not in cardiac failure. Since it is now proved that in congestive heart failure the intracranial pressure is markedly increased, the Cheyne-Stokes' respiration in some patients with cardiac disease may be explained in a similar manner. In other words, the increase in intracranial pressure may be the initial stimulus which calls forth Cheyne-Stokes' respiration in persons with cardiac failure. Further studies, which are now in progress, must be carried out before this can be shown to be true.

It has been shown by Cushing ¹⁴ that if the cerebrospinal fluid pressure rises to a certain level the arterial blood pressure likewise rises and that it tends to maintain itself above the level of intracranial pressure. It appears likely that one reason why hypertension not uncommonly develops in a patient in the later stages of congestive heart failure is that there is increased intracranial pressure brought on by the increased venous pressure of cardiac failure.

SUMMARY AND CONCLUSIONS

1. The cerebrospinal fluid pressure is markedly elevated in persons with congestive heart failure.
2. The cerebrospinal fluid pressure, except for slight variations, usually runs closely parallel to the venous pressure in the prone position in persons with cardiac failure and, as a rule, the average ratio between the spinal fluid pressure and the venous pressure (1.6) in the patient with cardiac disease corresponds closely to that in the normal person. In general, either may be predicted from knowing the other.

14. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension, *Am. J. M. Sc.* **124**:375, 1902; The Blood Pressure Reaction of Acute Cerebral Compression Illustrated by Cases of Intracranial Hemorrhage, *Am. J. M. Sc.* **125**:1017, 1903.

3. The fall in cerebrospinal fluid pressure usually runs closely parallel with the fall in venous pressure as the patient with cardiac failure regains compensation.

4. Spinal drainage in patients with congestive heart failure was followed by a fall in venous pressure in eight instances, by a rise in two instances and by no change in three instances. In the majority of cases spinal drainage was followed by a decrease in dyspnea.

5. The cisternal pressure is much less in patients in the sitting than in the prone position, although the systemic venous pressure and spinal fluid pressure are greater. This difference in cisternal pressure and hence in cerebral venous pressure is more pronounced in patients with cardiac failure; its bearing on orthopnea is discussed.

6. The relationship of the increased intracranial pressure to Cheyne-Stokes' respiration and hypertension in patients with congestive heart failure is discussed.

HEREDITY IN ARTERIOLAR (ESSENTIAL) HYPERTENSION

A CLINICAL STUDY OF THE BLOOD PRESSURE OF 1,524 MEMBERS OF
277 FAMILIES

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Heredity is the most important known factor in the development of arteriolar (essential) hypertension. Valuable evidence for this opinion can be secured by studying the blood pressure in a large number of hypertensive and nonhypertensive families, with an effort to obtain the blood pressure readings of all of the available relatives in two or more generations. This has been the purpose and method of the present study.

REVIEW OF THE LITERATURE

A definite relationship between heredity and arteriolar (essential) hypertension and its complications was noted long ago by Dieulafoy, Raymond, Broadbent, Gowers, Allbutt¹ and others. More recently, this relationship was further demonstrated by the results of systematic studies of family histories. In the studies, O'Hare, Walker and Vickers² and Weitz³ showed that a history of cardiovascular disease is frequent among the relatives of hypertensive patients. Weitz³ showed in addition that there was an abnormally high incidence of elevated blood pressure readings among the brothers and sisters of his hypertensive patients as compared with the frequency of elevated readings in the brothers and sisters of people with normal blood pressure.

Other evidence showing the close relationship between heredity and arteriolar hypertension consists of several reports of families in which the disease was prevalent. De Nador-Nikititch⁴ reported a family in

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1. Dieulafoy, M.: *Du rôle de l'hérédité dans la production de l'hémorrhagie cérébrale*, *Gaz. hebdomadaire de médecine*, **13**:594 (Sept. 22) 1876. Raymond, P.: *L'hérédité dans l'hémorrhagie cérébrale*, *Progrès médical*, **23**:196 (March 30) 1907. Broadbent, W. H.: *Heart Disease*, New York, William Wood & Company, 1898, p. 80. Gowers, W. R.: *Diseases of the Nervous System*, London, J. & A. Churchill, 1893, vol. 2, p. 386. Allbutt, C.: *Diseases of the Arteries, Including Angina Pectoris*, New York, The Macmillan Company, 1915, vol. 1, pp. 164 and 412.

2. O'Hare, J. P.; Walker, W. G., and Vickers, M. C.: *Heredity and Hypertension*, *J. A. M. A.* **83**:27 (July 5) 1924.

3. Weitz, W.: *Zur Aetiologie der genuinen oder vasculären Hypertension*, *Ztschr. f. klin. Med.* **96**:151, 1923.

4. de Nador-Nikititch, Etienne: *Sur l'étiologie de l'hypertension artérielle essentielle*, *Arch. d. mal. du cœur* **18**:582 (Sept.) 1925.

which he found hypertension in the one parent studied and in 5 of 8 children. He presented only one reading of the blood pressure in each person. Rosenbloom⁵ reported a family consisting of the parents and 10 children. He stated that 8 of the 10 children had arteriolar hypertension. The readings of the blood pressure were reported in only 4 of the 8 children. He also stated that the parents died of cerebral hemorrhage, but he did not present their blood pressure readings. Dawson⁶ described 2 families containing 3 and 5 members, respectively. In both of the families, representing two generations, elevated readings of the blood pressure were found in all of the members. Weitz⁷ reported 7 families, and Badía Brandia⁸ described 4, in all of which, by a combination of family history and blood pressure readings, they considered arteriolar hypertension present in at least one member of each of two or three generations. I⁹ recently reported a family in which I studied the blood pressure of every member for three generations, totaling 32 members above 13 years of age. It was found that 100 per cent of the first generation, 80 per cent of the second generation and 25 per cent of the third generation had elevated readings of the blood pressure on two or more visits. This apparently is the first family reported in which by direct study of the blood pressure elevated readings were found in three generations.

METHODS AND MATERIAL

Method.—It was decided that the most efficient way of examining the relatives of patients was to meet them when they came to the hospital to visit the patients. This method did not always permit the study of as many relatives of an individual family as did the earlier method of going to the homes, but it allowed the study of a much larger number of families and individuals. As a rule, the original patient in the hospital would explain the study to some of his relatives, who in turn would explain it to the others, so that when the relatives arrived, they knew what was to be done. On arrival at the hospital, the relatives were allowed to go to the patient's bedside and to rest and talk for a minimum of five minutes. The purpose of the study was then carefully explained to each relative so as to allay excitement as much as possible. Then, with the relative sitting in a chair and his arm resting on the patient's bed, the blood pressure was taken and a rough

5. Rosenbloom, J.: Familial Hypertension with Report of a Case, *J. Lab. & Clin. Med.* 8:681 (July) 1923.

6. Dawson: Hyperpiesis, *Brit. M. J.* 2:1161 (Dec. 19) 1925.

7. Weitz, W.: Ueber die Bedeutung der Erbmasse für die Aetiologie der Herz- und Gefässkrankheiten, Sonderabdruck über Hypertension (Aerztlicher Fortbildungskurs in Bad Nauheim, Pfingsten, 1926).

8. Badía Brandia, M.: El factor herencia en la etiología de la hipertensión esencial, *Rev. méd. de Barcelona* 13:3 (Jan.) 1930.

9. Ayman, D.: The Hereditary Aspect of Arteriolar (Essential) Hypertension, Report of a Family. *New England J. Med.* 209:194 (July 27) 1933.

estimation of the pulse rate was noted. Next, the person was asked his age, height and weight. The majority of the people knew their weight fairly accurately, and many of them knew their height. In cases in which the height was unknown, the subject was asked to stand, and his height was roughly gaged. The determination of the blood pressure was then repeated. In many cases, when the blood pressure readings were elevated, it was possible to check them on later visits. I made all of the readings, using a mercury sphygmomanometer. The end of the third (auscultatory) phase was taken as the criterion of diastolic blood pressure.

Material.—The blood pressure of 1,770 members of 345 hypertensive and non-hypertensive families was studied. The families of successive patients admitted to the surgical and medical wards of the Beth Israel Hospital were utilized without selection. However, in tabulating the results, many of the families had to be omitted because of inadequate data. Thus it was necessary to omit families in which only one parent was available, if this parent had a normal blood pressure, for the unavailable parent might have arteriolar hypertension. However, families were utilized in which arteriolar hypertension was found in the only parent available. Families were omitted in which both parents had normal blood pressure readings, if one of the parents was seriously ill, cachectic or markedly anemic, for such persons may have had a previous hypertension. Families in which one of the parents had nephritis or one of the parents stated that his blood pressure had been elevated in the past but at the time of the examination was normal were also omitted. These omissions reduced the total number of people included in the accompanying analysis to 1,524 and the total number of families to 277.

Method of Analyzing Results.—The families studied were grouped according to the presence or absence of arteriolar hypertension in one or both parents. In table 1, it is seen that the normal division (groups 1, 2, 3 and 4) consists of families in which both parents had blood pressure readings within the limits of normal.¹⁰ This normal division was divided into four groups on the basis of the age of the parents and the height of their normal blood pressures. Thus, groups 1 and 2 consist of families in which both parents were 50 years or more of age, but in group 1 both parents had blood pressure readings of less than 138 systolic and 90 diastolic, whereas in group 2 at least one of the parents had a blood pressure reading of from 140 to 150 systolic and of less than 90 diastolic. Groups 3 and 4 consist of families in which the mothers were 49 years of age or less, the blood pressure in group 3 being 136 or less systolic and 90 or less diastolic; in group 4, from 136 to 150 systolic and 90 or less diastolic. It should be noted that in group 4, in which the blood pressure is a high normal and the mothers are 49 years of age or less, some of these parents may develop arteriolar hypertension later. It should also be noted that, in this normal division, the blood pressure figures given in table 1 indicate the highest reading obtained for the parents, despite the fact that most of the parents had lower readings at the first or subsequent determination.

The intermediate division, groups 5, 6, 7 and 8, consists of families in which elevated blood pressure readings occurred in at least one of the parents on the first determination, but in which the readings were either normal or much lower on subsequent visits or were not repeated at all. The individual groups within this division have been based chiefly on the height of the blood pressure in the parents.

10. Rogers, O. H., and Hunter, A. W.: Mortality Study of Impaired Lives, Proc. A. Life Insur. M. Dir. America 10:43, 1923.

The definitely hypertensive division (groups 9, 10, 11 and 12) consists of families in which one or both parents had undoubted arteriolar hypertension on at least two visits and usually on many occasions. In these parents the blood pressure readings were all above 160 systolic and 90 diastolic. Thus, group 9 was composed of families in which one parent had arteriolar hypertension and the other parent either normal or questionably normal blood pressure. Group 10 consists of families in which one parent had arteriolar hypertension, while the other was not available

TABLE 1.—Analysis of 1,524 Patients and 277 Families Reported in This Study

Division	Family Group	No. of Parents Examined in Family	Age of Parents	Blood Pressure of Parents		No. of Families	Total No. of Parents	No. of Children Aged 14 to 39, Inclusive	No. of Male Children Aged 14 to 39, Inclusive	No. of Children Aged 40 or Over	No. of Brothers and Sisters of Parents
				Systolic	Diastolic						
Normal	1	2	51 or more	138 or less	Below 90	10	20	32	11	2	..
	2	2	50 or more	140 to 150	Below 90	15	30	52	25	0	..
	3	2	Females, 49 or less	136 or less	Below 90	35	70	77	37	0	..
	4	2	Females, 49 or less	136 to 150	90 or less	19	38	49	23	0	..
Intermediate	5	2	50 or more	150 to 170	100 or less	28	56	78	31	21	..
	6	2	Females, 49 or less	140 to 170	100 or less	10	38	46	19	0	..
	7	2	50 or more	170 to 190	100 or less	40	72	121	53	19	..
	8	2	50 or more	200 or more	118 or less	16	26	23	9	16	..
Hypertensive	9	2	All ages	Other parent normal	50	100	166	87	9	..
	10	1	50 or more	Essential hypertension* in one parent	Other parent unavailable	23	23	59	33	7	..
	11	1	58 or more	Other parent unavailable but has history of hypertension	8	8	32	15	5	..
	12	2	Chiefly over 50	Both parents have hypertension*		14	28	55	32	2	..
Total (1,524).....						277	489	780	375	79	176

* Over 160 systolic and 90 diastolic on two or more visits.

for examination and was not known to have an elevated blood pressure or cardiovascular disease. Group 11 was made up of families in which one parent had arteriolar hypertension, while the other parent, though not available for examination, was known either to be suffering from, or to have died of, arteriolar hypertension and its complications. Group 12 was composed of families in which both parents had arteriolar hypertension.

Finally, group 13, not presented in table 1, consisted of both normal and hypertensive families in which three generations were available for study.

The age, blood pressure, number of parents and number and sex of the children studied in each group are also presented in table 1.

TABLE 2.—Systolic Blood Pressure Readings of the 780 Children, Aged from 14 to 39, Inclusive, Arranged by Percentage Incidence in Each Family Group

Systolic Blood Pressure	Groups											
	Normal Parent(s)				Intermediate				Hypertensive Parent(s)			
	1	2	3	4	5	6	7	8	9	10	11	12
85-89	1.3
90-94	3.2	1.9	3.9	0.9	0.6	1.7
95-99	9.7	1.9	1.3	1.8	2.9	0.9	0.6
100-104	16.0	9.3	9.1	5.6	5.7	4.3	3.5	4.4	4.8	3.4	1.9
105-109	6.4	7.4	6.5	7.2	2.2	3.5	4.4	3.6	1.7	1.9
110-114	19.3	20.4	18.2	10.8	10.0	12.9	11.0	17.6	12.6	11.9	12.5
115-119	9.7	9.3	6.5	18.0	7.2	12.9	9.6	4.4	6.0	5.1	12.5	1.9
120-124	19.3	20.4	18.2	16.2	25.7	11.0	20.0	26.4	12.6	11.9	6.3	9.3
125-129	3.2	1.9	3.9	16.2	8.6	17.2	7.0	4.4	6.6	11.9	9.4	5.6
130-134	6.4	11.1	13.0	16.2	18.6	11.0	11.2	13.2	15.0	10.2	21.9	13.0
135-139	3.2	7.4	3.9	1.8	1.4	6.6	6.1	5.4	5.1	6.3	9.3
140-144	3.2	3.8	9.1	5.6	10.0	8.8	14.8	22.0	16.8	8.5	9.4	20.4
145-149	1.9	4.4	3.5	3.6	3.4	9.4	5.6
150-154	1.9	2.6	8.8	2.7	7.2	10.2	6.3	14.8
155-159	1.9	2.9	4.3	0.9	0.6	5.1	5.6
160-164	1.3	2.2	1.8	2.4	5.1	6.3	3.7
165-169	1.7
170-174	1.8	3.7
175-179
180-184	0.6	1.7
185-189	1.9
190-194	0.9
195-199
200-204	1.7	1.9
Percentage incidence												
Above												
139 mm. Hg	3.2	9.5	13.0	5.6	12.9	28.5	24.6	22.0	32.8	37.4	31.4	57.6
144 mm. Hg	0.0	5.7	3.9	0.0	2.9	19.7	9.8	0.0	16.0	28.9	22.0	31.6
Below												
105 mm. Hg	28.9	13.1	15.6	7.4	8.6	4.3	5.3	4.4	6.0	5.1	0.0	1.9

TABLE 3.—Diastolic Blood Pressure Readings of the 780 Children Aged from 14 to 39, Inclusive, Arranged by Percentage Incidence in Each Group

Diastolic Blood Pressure	Groups											
	Normal Parent(s)				Intermediate				Hypertensive Parent(s)			
	1	2	3	4	5	6	7	8	9	10	11	12
40-49	3.2
50-54	15.5	3.8	1.4	2.7	1.8
55-59	3.1	3.8	2.7	3.8	3.2	2.2	0.9	4.4	1.2	1.7
60-64	13.5	13.4	15.2	7.7	6.4	4.3	6.3	17.6	12.0	10.2	1.9
65-69	6.2	23.0	17.5	5.8	7.8	11.0	6.3	13.2	6.0	1.7	6.6	3.7
70-74	37.2	32.6	20.8	19.2	26.5	24.2	27.9	17.6	21.6	18.7	9.9	13.0
75-79	9.3	7.7	12.5	17.3	7.8	15.4	13.5	17.6	9.6	18.7	16.5	16.7
80-84	6.2	21.1	22.2	23.0	21.8	8.8	23.0	22.0	18.0	24.8	23.1	29.6
85-89	3.1	1.9	5.5	5.8	15.6	8.8	8.1	8.8	11.4	10.2	26.4	3.7
90-94	7.7	5.5	5.8	7.8	6.6	9.0	14.5	11.9	13.2	16.7
95-99	3.1	1.9	6.6	0.9	1.8	9.3
100-104	1.9	1.6	2.2	0.9	1.8	1.7	3.3	3.7
105-109	2.2
110-114	0.9
115-119
120-124
125-129	1.7	1.9
130-134
135-139	0.9
140-144	0.9
Percentage incidence												
Above												
84 mm. Hg	6.2	13.4	11.0	11.6	25.0	26.4	21.6	8.8	29.5	25.5	42.9	35.3
Below												
60 mm. Hg	18.6	7.6	4.1	3.8	6.4	2.2	3.6	4.4	3.0	1.7	0.0	0.0

BLOOD PRESSURE READINGS IN CHILDREN

Analysis by Family Groups of All the Blood Pressure Readings.—In tables 2 and 3 are presented the systolic and diastolic blood pressure readings of the children arranged according to family groups. They were the highest systolic and diastolic readings found for the individual person on the first visit. The figures in the tables indicate the percentage incidence of the blood pressure readings for each rise of 5 mm. of mercury in systolic and diastolic blood pressure. In these tables it is seen that above a systolic level of 139 mm. or a diastolic level of 84 mm. there was a markedly higher incidence of blood pressure readings in the children of the hypertensive division than in those of the normal groups. For example, table 2 shows that the incidence of systolic blood pressure readings above 139 mm. rose from 3.2 per cent for the strictly normal persons (group 1) to 57.6 per cent for the hypertensive persons (group 12). If one averages the incidence for each division of four groups, it is found that 7.9 per cent of the children of the normal division, 21.8 per cent of the intermediate division and 39.8 per cent of the hypertensive division had systolic blood pressure readings above 139 mm. If one determines the percentage of systolic readings above 144 mm., the differences are even more striking, showing 2.4 per cent for the normal, 8.1 per cent for the intermediate and 24.6 per cent for the hypertensive division. Similarly, if one takes a dividing level of 84 mm. for the diastolic blood pressure, it is found that in the normal division (groups 1, 2, 3 and 4) 10.6 per cent of the readings were above 84 mm.; in the intermediate division, 20.5 per cent, and in the hypertensive division, 33.3 per cent (table 3).

In contrast, the incidence of systolic readings below 105 mm. and diastolic readings below 60 mm. was much higher in the normal division than in the hypertensive division. The tables do not indicate how often elevated systolic and diastolic readings occurred together in the various groups.

Incidence of Simultaneously Elevated Systolic and Diastolic Readings.—The occurrence of both an elevated systolic and an elevated diastolic blood pressure in the same person is probably more important than the occurrence of either an elevated systolic or an elevated diastolic blood pressure alone. In this part of the analysis, a blood pressure of 140 systolic, and 80 diastolic, or higher, was considered above normal for persons between the ages of 14 and 39.¹⁰ In reality, most of the people to be discussed in this section had blood pressure readings well above 140 systolic and 80 diastolic. Referring to table 4, it is seen that the incidence of elevated blood pressure readings in the children, as determined for each group of parents, shows a striking increase as one goes from the groups with normal parents to those with hypertensive parents. Thus, in group 1, which was composed of families in which both parents

had absolutely normal blood pressure readings and were over 50 years of age, the incidence of elevated blood pressure readings in the children was only 3.1 per cent; that is, only 1 of the 31 children in this group. Turning to the other group of extreme cases, group 12, in which both parents had undoubted arteriolar hypertension, one finds a striking incidence of elevated readings in the children, amounting to 45.4 per cent, that is, 25 of 55 persons. A similar striking difference is seen on comparing the incidence in each division of family groups, the incidence of elevated readings in the normal division (groups 1, 2, 3 and 4) being 5.5 per cent; in the intermediate division, 17.1 per cent, and in the hypertensive division, 31.9 per cent. It is to be noted that in group 5, composed of parents who were over 50 years of age, at least one of

TABLE 4.—Incidence in 780 Children of Elevated Blood Pressure Readings of 140 Systolic and 80 or More Diastolic

Family Group	Children Studied, Aged 14-39, Total Number	Children with Blood Pressure 140/80 or More	
		Number	Percentage of Total
1	32	1	3.1
2	52	3	5.8
3	77	4	5.2
4	49	4	8.2
Total	210	12	Average 5.5
5	78	6	7.7
6	46	9	19.5
7	121	18	14.9
8	23	6	26.0
Total	268	39	Average 17.1
9	166	47	28.3
10	59	17	28.8
11	32	8	25.0
12	55	25	45.4
Total	312	97	Average 31.9

whom showed on the first visit blood pressure readings of from 150 to 170 systolic and of 100 or less diastolic, the incidence of elevated readings in the children was only 7.7 per cent.

Analysis of the Group of Children with Elevated Blood Pressure Readings (140 Systolic and 80 or More Diastolic).—As seen in table 4, there were 148 children with blood pressure readings of 140 systolic and 80 diastolic, or higher. In reality, 75 of the 148 children had systolic blood pressures of 150 or more, and 30 of the 148 had systolic readings of 160 or more. In 84 of the 148 children, the diastolic blood pressure was 90 mm. or more; in 27 it was 96 mm. or more, and in 17 it was 100 mm. or more. Blood pressure readings had been made before by other physicians in 118 of the 148 children, and 19 of these 118 knew that their blood pressure was elevated at the time. Sixty-two of the 148 were seen by me on a second visit, and at this time 40 of the 62 still

showed elevated blood pressure readings. In 18 of the 148, it was noted that a rapid pulse was present while the blood pressure was being taken.

The weight of the children with elevated blood pressure readings as compared with the weight of the children with normal blood pressure readings is presented in table 5. All of the normal children whose weights are presented in table 5 had blood pressures of 130 systolic and 84 diastolic, or less. It is seen that in the hypertensive division, 97 children with elevated readings had an average weight of $13\frac{1}{5}$ pounds (6 Kg.) above the normal for their sex, age, and height,¹¹ while 115

TABLE 5.—*The Average Weight of "Hypertensive" Children as Compared with Normal Children*

Family Division	"Hypertensive" Children		Normal Children	
	Number	Pounds Above Normal	Number	Pounds Above Normal
Normal.....	12	+ 8.1	154	+4.2
Intermediate.....	39	+14.2	115
Hypertensive.....	97	+13.2	115	+4.8
Total.....	148		269	
Average.....		+14.3		+4.5

TABLE 6.—*Average Age of "Hypertensive" Children, as Compared with All of the Children*

Family Groups	Average Age of All Children, Years		Average Age of Hypertensive Children, Years	
1.....	25.5	23.0		22.1
2.....	26.3			
3.....	20.2			
4.....	10.9			
5.....	26.5	26.2	25.8	26.5
6.....	20.9		20.0	
7.....	27.8		29.4	
8.....	29.5		30.6	
9.....	26.0	26.8	28.2	28.7
11.....	25.9		26.5	
11.....	28.8		32.3	
12.....	26.4		27.8	

normal children in the hypertensive division were only $4\frac{1}{10}$ pounds (2.1 Kg.) above normal. The average weight for the 148 children with elevated readings was $14\frac{3}{10}$ pounds (6.48 Kg.) above the normal, and for 269 normal children it was $4\frac{1}{2}$ pounds (2 Kg.) above the normal.

Table 6 shows that the average age of the children with elevated readings in each group was strikingly similar to that of all of the children in the groups.

11. Metropolitan Life Insurance Company, Study of the Weight of 200,000 Insured Individuals.

The incidence of elevated blood pressure readings by sex is seen in table 7. In this table it is first to be noted that there was a fairly equal distribution of the sexes among the 780 children studied. On the other hand, the comparatively small number of children with elevated readings made their average of little significance. In general, there was, roughly, as high an incidence of elevated readings in the males as in the females, though it was perhaps slightly higher in the males. Thus, of 148 patients with elevated readings, 91 (61.5 per cent) were males.

Questionably Elevated Blood Pressures.—There were 47 children who had either an elevated systolic reading or an elevated diastolic reading, but not both. The group with elevated systolic readings alone had systolic readings of 140 or higher, and diastolic readings below 80 mm. There were 28 such persons, in 24 of whom the systolic read-

TABLE 7.—*Sex Incidence in the Normal Children as Compared with that in Children Having Elevated Blood Pressure Readings*

Family Group	Males in the 780 Children, per Cent	Males in the 148 Hypertensive Children, per Cent
1.....	46	0
2.....	51	66.6
3.....	48	66.6
4.....	34	50.0
5.....	46	33.3
6.....	50	66.6
7.....	45	72.0
8.....	39	33.3
9.....	51.7	72.0
10.....	32.2	41.0
11.....	50.0	75.0
12.....	59.0	60.0

ings were between 140 and 144, and in the remaining 4 from 145 to 156. In 27 of the 28 children, the diastolic readings were between 70 and 78 mm. Whenever a high pulse pressure was encountered in the children, auscultation of the heart was practiced, and in this way 3 cases of aortic regurgitation were discovered; they were omitted from the figures. There were 19 children whose diastolic readings were between 90 and 94 mm. and whose systolic readings were between 130 and 138. In general, the children with either elevated systolic or elevated diastolic readings occurred in the same frequency in the normal, intermediate and hypertensive divisions.

BLOOD PRESSURE READINGS OF THE BROTHERS AND SISTERS OF THE PARENTS

It was possible to study the blood pressure of 176 brothers and sisters of the children's parents. Twenty of the 176 had questionably elevated blood pressure readings and were not included in the results. Of the remaining 156 (table 8), 70 were brothers and sisters of the

parents with normal blood pressure, and 86 were brothers and sisters of the parents with arteriolar hypertension. As seen in table 8, 37.3 per cent of the brothers and sisters of the normal parents had definitely elevated blood pressures as compared with the normal standards,¹⁰ whereas 65.3 per cent of the brothers and sisters of the hypertensive parents had elevated readings.

FAMILIES IN WHICH THREE GENERATIONS WERE STUDIED

There were 18 families in each of which three generations were studied. The individual parts of each of these families, consisting of one or more parents with children, have already been included in the family groups already analyzed. It was not possible to study all the members of the three generations, as in the detailed study of the family of three generations recently reported by me.⁹ It was possible, however, to study 185 members of the 18 families. In 16 of the 18 families, there was

TABLE 8.—*Incidence of Elevated Blood Pressure Readings in the Brothers and Sisters of the Parents*

	Number with Normal Blood Pressure	Number and per Cent with Elevated Blood Pressure
Brother and sisters of parents with normal blood pressure	51	19 (37.3%)
Brothers and sisters of parents with arteriolar hypertension	32	54 (65.3%)

definite arteriolar hypertension in one or both grandparents studied, that is, the first generation. The second generations of these 16 families were composed of 59 persons, 30 of whom had definitely elevated systolic and diastolic blood pressure readings. In the third or youngest generations that were studied, there were 37 persons, 8 of whom had elevated systolic and diastolic readings. Of the two families in which the grandparents (first generation) had normal blood pressure, all 7 members of the second generations had normal blood pressure. Although the entire present study is based on actual blood pressure readings, it is interesting to note that in 3 of these families of three generations, the family history in the great-grandparents, or fourth generation was positive for cardiovascular disease.

Although no systematic analysis of the personalities or body-build of these persons was made, it was noted that a large number of the hypertensive children in the present investigation were of the highstrung hyperactive type described in a previous investigation of hypertensive persons.¹² They usually resembled their hypertensive parent in this respect. In addition, like their hypertensive parent, they were most often of the sthenic type.

12. Ayman, D.: The Personality Type of Patients with Arteriolar (Essential) Hypertension, *Am. J. M. Sc.* **186**:213 (Aug.) 1933.

SUMMARY

To determine more clearly the presence of a familial or hereditary factor in arteriolar (essential) hypertension, a direct study of the blood pressure, height and weight of 1,524 members of 277 families was made.

It was found that in 780 members, aged from 14 to 39 years, of the second generation of the families, elevated systolic and diastolic blood pressure readings (140 systolic and 80 diastolic, or higher) occurred in 148 subjects. These 148 subjects had the same average age and sex incidence as the entire group of 780 children, but they were $14\frac{3}{10}$ pounds above the average weight compared to $4\frac{1}{2}$ pounds above the average weight for the normal children.

The families studied were then grouped according to the presence or absence of arteriolar (essential) hypertension in one or both parents. In the families whose parents had absolutely normal blood pressures, the incidence of elevated blood pressures in the children was only 3.1 per cent. In the families in which one parent had arteriolar hypertension, the incidence of elevated readings in the children rose to 28.3 per cent. In the families in which both parents had arteriolar hypertension the incidence of elevated readings in the children reached the striking level of 45.5 per cent.

Of 70 brothers and sisters of parents with normal blood pressures, 37.3 per cent had elevated blood pressure readings, whereas of 86 brothers and sisters of parents with arteriolar hypertension, 65.3 per cent had elevated blood pressure readings.

Finally, I studied 18 families in which parts of three generations were available and found the results strikingly similar to those given in the preceding paragraph.

The results presented show that there is an unusually high incidence of elevated blood pressure readings in the children, brothers, sisters and parents of subjects with arteriolar hypertension, as compared with similar relatives of subjects with normal blood pressure. These results are strong evidence for the existence of a hereditary factor in arteriolar (essential) hypertension.

371 Commonwealth Avenue.

News and Comment

EDWARD M. GIBBS MEMORIAL PRIZE

It is announced by the New York Academy of Medicine, 2 East One Hundred and Third Street, that a sum of approximately \$800 is available under the Edward M. Gibbs Memorial Prize toward original research in diseases of the kidney during 1934. Candidates, who must be physicians who have been graduated at least three years and residents of the United States, shall submit "Evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney." The award may be continued through not more than three years to any one person. Applications with the required evidence should be addressed to the New York Academy of Medicine prior to June 1.

MEETING OF AMERICAN HEART ASSOCIATION

The Tenth Scientific Session of the American Heart Association will be held on Tuesday, June 12, 1934, at the Cleveland Hotel, Cleveland. The program will be devoted to arteriosclerotic heart disease.

Book Reviews

Handbuch der allgemeinen Hämatologie. Edited by Hans Hirschfeld and Anton Hittmair. Volume II, part 1. Price, 55 marks. Pp. 700, with 259 text figures and 4 colored plates. Berlin: Urban & Schwarzenberg, 1933.

Volume I of this handbook has already been reviewed (*ARCH. INT. MED.* **52**:821 [Nov.] 1933). Volume II, part 1, deals with the technic of examination of the blood. Part 2, which remains to be published, will be devoted to a consideration of the blood plasma.

The technic of examination of the blood is covered in a series of twenty-three monographs, two of which have been written by Hirschfeld, the senior editor, and nine by Hittmair, while the remaining chapters are supplied by eight German contributors and one Danish contributor.

In the first chapter (Hittmair, pages 1 to 16), elementary information concerning methods of obtaining blood is presented in considerable detail. The description of methods of collecting blood from various animals will be found useful. Surprisingly brief attention is given to the examination of fresh blood (Hittmair, pages 17 to 19), and its importance in the demonstration of sickling is not even mentioned. In the third chapter (Hittmair, dark-field examination, pages 21 to 28), ultramicroscopy is briefly discussed.

Under the title "Theory of Staining" (pages 29 to 94) Mommsen has written a detailed monograph on the chemical and physicochemical aspects of the staining of blood. In the following chapter (pages 95 to 118) Hirschfeld and Moldavsky discuss at length the staining and significance of reticulocytes and devote several pages as well as three colored plates to the supravital staining of leukocytes with azure II. Sabin's method, however, is dismissed with half a page of technical description and the statement that "the method is no longer recognized as an accurate means of differentiating between monocytes and other mononuclear forms and has been rejected, among others, by Naegeli." Even those who have not subscribed to the enthusiasm exhibited by Sabin's followers must be surprised at this cursory treatment of her work.

The measurement of the size (actually, diameter) of the formed elements of the blood (Hittmair, pages 119 to 124) is given attention so brief as to be out of proportion to the unrestricted length of most of the chapters in this handbook. The Price-Jones method, which is at least of historical interest, has been ignored.

A chapter on the staining of dry preparations (Hittmair, pages 125 to 168) and the special section on the demonstration of the intracellular ferments of leukocytes (Hirschfeld, pages 169 to 175) are replete with details and bring together useful information concerning a great variety of special stains. The discussion of the methods and technic of cytodagnosis (Zadek, pages 177 to 196) supplements the excellent monograph on transudates and exudates by the same author in volume I. In the succeeding chapter (pages 197 to 228), methods of obtaining, fixing, decalcifying, mounting and staining bone marrow are ably reviewed by Petri, and a variety of special stains is described.

Hittmair discusses methods of hemoglobin determination and cell counting at great length (pages 239 to 318). The lack of a satisfactory method for hemoglobin determination is well illustrated by the number of instruments devised for this purpose. Hittmair has found it impossible to include them all within thirty-six pages. Methods of blood counting and a great variety of hemacytometers are described in detail. Yet nothing is said about the historical development of blood counting, and one notes the omission of mention of the Bass-Johns chamber and such a generally used diluent for platelet counting as Rees and Ecker's solution. A great variety of hemoglobin indexes is recapitulated, but, in the opinion of the reviewer, this simply makes confusion. One would welcome some critical evaluation by the author.

An excellent critical discussion of hematocrit methods is presented in the chapter on the determination of red cell volume (Heilmeyer, pages 345 to 372),

and a great variety of indirect methods is described and critically evaluated. The chapter on the technic of blood sedimentation (Leffkowitz, pages 435 to 490) is perhaps the best available review of the subject and leaves no room for criticism. The section devoted to the fragility of the red corpuscles (Simmel, pages 495 to 584) is detailed and offers considerable information for the clinical hematologist. The latter will also find the chapter on blood coagulation (Schultz, pages 645 to 700) of value, particularly on account of the description of infrequently used methods, many of which are unknown in this country.

Chapters on the determination of the specific gravity (pages 329 to 344) and the viscosity (pages 373 to 406) of blood and on refractometry (pages 407 to 434), all by Heilmeyer, include considerations of physical principles, methods, normal values and influencing factors. Schumm contributes a section on the spectroscopic and spectrographic examination of blood (pages 585 to 618).

Mertens discusses in detail the qualitative and quantitative determination of bilirubin (pages 619 to 644). Short sections are devoted to the guttadiaphot (Hittmair, pages 491 to 494), the photography and drawing of microscopic preparations (Hittmair, pages 229 to 238) and the methods of calculating error and probability in hematologic technic (Hittmair, pages 319 to 328).

The writers of this treatise have succeeded in bringing together a wealth of information which previously was scattered in such a variety of journals as to be accessible only through much loss of time. Extensive bibliographies make this an important reference work. Unfortunately, emphasis is given to the German literature, and American contributions are somewhat inadequately considered. In several chapters the discussion is so elementary and verbose as to detract seriously from the usefulness of the information. A critical evaluation of methods, which the writers' experience should have permitted them to make, is frequently sought for in vain. Although the typography is good, a more liberal use of heavy type would have facilitated the quick selection of information. In comparison with the usefulness of this handbook, these objections are not, however, of great importance. Both the teacher and the investigator will find this book invaluable.

Pediatrics. By Henry Dwight Chapin and Lawrence T. Royster. Seventh edition, revised and rewritten by Lawrence T. Royster. Price, \$7. Pp. 775. Baltimore: William Wood & Company, 1933.

The ideal textbook of pediatrics is one which confines itself to those conditions peculiar to childhood and to the special manifestations of disease in children. Adequate and for that matter outstanding texts of general medicine are always readily available; to duplicate in treatises on pediatrics discussions of infectious disease, neurology and dermatology, except so far as the picture is significantly modified by the preadolescent state, seems ill advised and superfluous. Granted that practical considerations limit the size of ordinary textbooks to approximately 1,000 pages, then if matters of growth, development, infant feeding and special conditions of childhood are properly dealt with, insufficient space remains in which to do justice to general medicine, neurology and dermatology. The result is that what is said about typhoid fever, diabetes insipidus or multiple sclerosis may be too brief to be of use to one unfamiliar with the subject and yet too commonplace to interest or instruct those of even scant experience.

Whether or not the foregoing thesis is sound in principle, the fault of construction to which allusion has been made is evident in the present work. The chapters on growth and development, on the appraisal of the child, on injuries sustained at birth and diseases and abnormalities of the new-born, on the technic of examination, on infant feeding and on the care of premature infants are instructive and satisfying. This part of the treatise is clearly written with enthusiasm and *savoir de metier*. The later sections, however, beginning with that on infectious disease, are disappointing; they consist of brief and inadequate summaries of what is better said in almost any current textbook of medicine. It is always easy for the reviewer to quarrel about minor points. One might

disagree, however, with the claim that the Bordet-Gengou bacillus is the specific organism of whooping cough in the face of the evidence recently brought forward by Rich and others in favor of an ultravirus. Even more disturbing is the view that influenza is most probably caused by "a mixed infection, with streptococcus predominating." That the authors are not soundly informed on current views of etiology of infectious disease is further borne out by their confused statements on erysipelas and acute tonsillitis, both now proved to be due to hemolytic streptococci. Fundamental concepts of tuberculous infection are dismissed with a few brief and inadequate paragraphs, and the evidence recently confirmed by Dochez that the common cold is caused by a filtrable virus appears to be unfamiliar to the writers. In the midst of the chapter on infectious disease one finds a heading "Rheumatoids" under which chronic arthritis is briefly discussed, and one is even more surprised in the section on ductless glands to encounter diseases of the spleen, Hodgkin's disease, acute and chronic adenitis and other irrelevant conditions. Diabetes insipidus, on the other hand, is discussed with disorders of the urine and kidneys. The sections on nephritis are wholly inadequate. "In attempting to classify the various forms of nephritis . . . the student at the bedside will be much confused." This confusion seems to exist equally in the minds of the writers, and certainly no remedy is brought out in the text.

On the whole, the reviewer believes that the subject could be treated in a more satisfactory manner; however, the writers' broad personal experience is evident, and the book will doubtless continue to be useful to those looking for clinical guidance in pediatrics.

Diabetes Mellitus. By I. M. Rabinowitch, M.D. With an introduction by A. M. MacCallum. Price, \$3.50. Pp. 246. Toronto, Canada: The Macmillan Company of Canada, Ltd., 1933.

This book is written for the student in the medical school and for the practitioner. It covers in a concise way the principal features of diabetes with little reference to the physiology involved or other subjects of academic significance. In the matter of treatment stress is laid on the essentials; "the description of a method of treatment without a knowledge of blood sugar and alkali reserve, or the use of scales and without a detailed knowledge of the value of materials, is in the writer's opinion one of the chief justifications of the present publication."

The author has made use of an ingenious system of food models and standard measures to replace the unjustifiably expensive food scales. He has also abandoned the well known food tables in favor of lists of substitutions. His basic diet contains, in most cases, from ten to twelve average sized slices of bread, and the substitutions provide an equivalent amount of carbohydrate, including sweets, honey, jam and sugar. To enable the utilization of the high carbohydrate allowance without resort to prohibitive amounts of insulin, but mainly because it is supposed that a certain degree of undernutrition is desirable in diabetes, the total calories of the diet are restricted by rigid limitation of the allowance of fat. Limitation of fat is defended also on the supposititious ground that fat is injurious, a conclusion which is at best contentious. According to the text, "very few diabetics in the past had the disease for more than five years without the development of arteriosclerosis." The restriction of fat and calories which is imposed must detract considerably from the palatability of these diets, not to speak of the question of adequacy from the standpoint of meeting normal nutritional requirements.

The value of the book is considerably diminished by a somewhat dogmatic manner of presentation. An apology for this is offered, namely, that the author's experience in teaching has taught him "that if a handbook is to be useful it should contain that which the student can take with him on the date of graduation and make immediate use of." A wiser educational policy, in the mind of the reviewer, is one which encourages the critical attitude, particularly in the realm of therapy, where fashions change so frequently. The student might well be taught that methods of treatment which differ more or less radically may be used success-

fully by different physicians, and that methods successful in the hands of one may be less satisfactory when applied by another. This dictum seems to apply with special force to the treatment of diabetes.

Biochemistry of Medicine. By A. T. Cameron, Professor of Biochemistry, University of Manitoba, and C. R. Gilmour, Professor of Medicine, University of Manitoba. Price, \$5.50. Pp. 506. New York: William Wood & Company, 1933.

Physicians and students of medicine receiving clinical instruction will find this book an invaluable aid in applying biochemistry to the practice of medicine. Approximately one fifth of the book is devoted to a summary of the present state of knowledge of the chemistry of carbohydrates, fats and proteins and of intermediary metabolism. The physician who has not kept up with the developments in biochemistry will find this book readable and worth reading. It has less value for the advanced student of medicine, since he has had a more comprehensive course. The remaining four fifths deals with the medical applications of biochemistry. The headings of some of the chapters are: "The Reduction Test for Urine and What It Connotes," "Non-Diabetic Glycosurias," "Diabetes Mellitus," "Abnormal Fat Metabolism," "The Albuminuria Test and What It Connotes," "Abnormal Metabolism of Proteins and Protein Derivatives," "Metabolism of Water" and "Liver Functions and Liver Functional Tests." The book contains a large amount of information which the physician needs. The authors have attempted to make the book readily usable by the physician. They have avoided controversial material, generally giving only the view which is most commonly accepted. Very little historical material is given. Sufficient references are given to assist the reader in finding significant articles in journals, but no attempt is made to give a complete bibliography. There is a brief summary at the end of most of the chapters. Research men looking for a comprehensive survey of the medical applications of biochemistry will look elsewhere.

The reviewer believes that the section on the chemistry of carbohydrates is not written as successfully as the remainder of the book. For example, the attempt to simplify the chemistry of dextrose by referring to it as a derivative of methyl alcohol and formaldehyde is unnecessary and confusing. Structural formulas could have been used more effectively than they were. The ring structure of dextrose which is now generally accepted is given in a footnote. Also, the reviewer believes that there is unnecessary repetition in the first one fifth of the book.

The book is a contribution to the medical literature, and physicians and students of medicine will find it an excellent aid in correlating biochemistry and medicine.

Les rythmes et la vie. By Laignel-Lavastine, A. M. Chanoz, J. Monchanin, G. Richard, J. Guittou, F. Mentré, H. Duprat, H. Cardot and R. Biot. (Groupe lyonnais d'études médicales, philosophiques et biologiques.) Paper. Price, 15 francs. Pp. 261. Lyon: Librairie Lavandier, 1933.

The introduction to this book explains that it is an effort on the part of its nine collaborating authors to synthesize the results of their work in diverse fields; these range from astronomy to subatomic physics. The result is rather more than popularized science; it is nearer philosophy in the Spencerian sense. Of the sections which have special medical interest, one in particular is likely to fascinate but irritate the medical reader. It is entitled "The Cosmic Influx and Human Life," and it summarizes the theory and assumed facts of astrology. General ignorance of the relations of physiology to meteorology makes it difficult to criticize the author's arguments in detail. The ancient vocabulary of quadratures, ascending nodes, conjunctions and oppositions at once prejudices the modern reader. But the author of this section, Duprat, does not alter his vocabulary to mollify his reader's prejudice; he rather provokes it further by citing details from the works of Maag, Krafft and others, and by suggesting that physicians may yet find it profitable to consider the phases of the moon before administering a drug.

Certainly there is an urgent need for more concrete and reliable information as to the effects of climate, season and weather on human beings in health and in disease. Although research of this kind is going on in this country, much more is needed, and much of it should be directed specifically to the questions raised by Duprat. The weakest part of the book is a section on nervous and endocrine rhythms. Here one finds, for instance, a statement that "it is easy to distinguish a physiogenic from a psychogenic anxiety state by the p_H of the urine." It is unnecessary to point out here how much harm can result from putting such controvertible statements into the popular literature. Taken as a whole, the book has a strong appeal as general reading.

Les hémorrhoides. By Jean Rachet, Physician to the Hospitals of Paris. Price, 25 francs. Pp. 80, with 16 illustrations. Paris: Gaston Doin & Cie, 1933.

This short monograph on the diagnosis and treatment of hemorrhoids is a fasciculation of a French system of practical medicine now appearing under the title of "La pratique médicale illustrée" and edited chiefly by Prof. E. Sergent of Paris. This particular article lives up to the title of the system and discusses hemorrhoids in a practical and interesting manner.

The author comments on the frequency of the disorder and on its inherent mildness. He describes how to examine the recto-anal region and the use of the anoscope, emphasizing how important it is for physicians to become familiar with such examinations and to recognize early malignant or possibly malignant lesions. He discusses treatment competently. He lays considerable stress on the general measures of hygiene which can be instituted to minimize the severity and occurrence of hemorrhoids. His local treatment is reasonable. He believes that sclerosing injections offer the best form of surgical treatment now available, and he describes the technic of such injections in detail. He is not especially enthusiastic regarding results obtained from the various electrical forms of therapy which have been devised, and advocates using but rarely more radical surgical procedures. On the whole, he has assembled a chapter on hemorrhoids which should prove an asset to the system of medicine for which it was written.

RESIDUAL HEPATIC DAMAGE IN CATARRHAL JAUNDICE AS DETERMINED BY THE BILIRUBIN EXCRETION TEST

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AND

MOSES PAULSON, M.D.

BALTIMORE

Patients who have had catarrhal jaundice not infrequently manifest digestive complaints long after the attack of jaundice has subsided. The fact that on clinical investigation the patients present no detectable abnormalities has led to the impression that the symptoms are functional. An attempt to inquire whether residual hepatic damage rather than psychogenic factors may be responsible for these symptoms has led to this investigation.

By catarrhal or common infective hepatic jaundice is meant the condition as it is commonly understood and as it is described by Holt and Howland¹ and Rolleston and McNee.² It is a disease which is usually benign and probably caused by some unknown infection of the hepatobiliary system. It occurs sporadically or in epidemics independently of, or in association with, an acute infectious process. The anatomic features are not well known, since few cases which may safely be regarded as of this type come to necropsy. The condition is characterized clinically by gastro-intestinal symptoms, pyrexia and malaise and sometimes by mild prostration and abdominal pain. On examination, jaundice, an enlarged, tender liver, sometimes a palpable spleen, feces which may or may not appear acholic and bile pigments in the urine are noted. In addition, all of the other known causes of jaundice are eliminated. The duration of catarrhal jaundice usually varies from two weeks to two months. Not infrequently there are recurrences. A serious complication in rare instances is acute necrosis (yellow atrophy) of the liver.

MATERIAL AND METHOD

Material.—Cases in which a diagnosis of catarrhal jaundice had been made, in three instances within one year, and in eight instances within from three to

From the Department of Medicine, Chemical Division, and the Gastro-Intestinal Clinic, Johns Hopkins University and Hospital.

1. Holt, L. E., and Howland, John: *Diseases of Infancy and Childhood*, ed. 10, New York, D. Appleton and Company, 1933, p. 332.

2. Rolleston, Humphrey, and McNee, J. W.: *Diseases of the Liver, Gall-Bladder and Bile Ducts*, ed. 3, New York, The Macmillan Company, 1929, p. 596.

eighteen years prior to this study, were carefully selected from the records of the Johns Hopkins Hospital ward and outpatient departments. The records of the patients indicated that the clinical criteria outlined in the foregoing paragraph had been observed. Six patients (cases 2, 3, 4, 8, 9 and 10 in the table) presented no symptoms in the interval between the end of the acute illness and this study. The other five patients complained of weakness, lassitude, headache and vague digestive symptoms of a severity not sufficient to cause them to seek medical aid voluntarily.

Our series comprised eleven cases. A careful history was obtained from each patient, and a complete physical examination was made, including studies of the urine, stool and blood. In the cases in which the procedures were possible, cholecystography (with orally administered dye) and duodenal drainage were done

Data on Eleven Patients with Catarrhal Jaundice of Varying Duration

Case	Age of Patient	Duration of Jaundice	Interval Between Jaundice and Test, Years	Results of Physical Examination*	Results of Cholecystography	Results of Duodenal Drainage	Van den Bergh Reaction	Bilirubin Retention, per Cent
1	27	2 weeks, ambulatory	7	Essentially negative	Normal	Negative	Negative	11.3
2	9	3 weeks, ambulatory	3	Essentially negative	Faint indirect trace	0.0
3	53	11 days, ambulatory	$\frac{1}{2}$	Essentially negative	Normal	Negative	Negative	10.7
4	25	7 days, ambulatory	1	Essentially negative	Normal	Negative	Indirect trace	16.2
5	22	15 days, ambulatory	3	Essentially negative	Normal	Negative	Indirect trace	39.5
6	16	2 weeks, ambulatory	8	Underweight, secondary anemia	Subnormal concentration of dye	Indirect trace	50.0
7	16	10 days, ambulatory	5	Secondary anemia	Normal	Faint indirect trace	22.0
8	40	6 weeks, hospitalized	18	Not done	Negative	Negative	19.0
9	33	4 weeks, hospitalized	8	Essentially negative	Negative	0.0
10	42	4 weeks, hospitalized	$\frac{1}{4}$	Essentially negative	Normal	Negative	Faint indirect trace	22.1
11	23	3	Essentially negative	Normal	Negative	Negative	16.7

* Performed at the time that the bilirubin test was made.

to determine if disease of the gallbladder existed. The van den Bergh reaction and the bilirubin excretion test were then performed.

The commonly used tests of hepatic function are mainly of three types: (1) those, such as the van den Bergh reaction, used to detect the retention of bile pigments in the blood; (2) those depending on the ability of the liver to excrete dyes, such as bromsulphalein, bengal rose and phenol-tetra-chlor-phthalein when introduced intravenously, and (3) those determining the metabolic activity of the liver cells, such as the levulose and galactose tolerance tests.

The van den Bergh test was used in this study for comparative purposes. The aforementioned dye tests were not employed, since they are of relatively little value except when gross hepatic changes are present. The galactose tolerance test is of value only in the differential diagnosis of jaundice. Our cases were free from icterus. The same objection holds for the levulose tolerance test as for the dye

tests of hepatic function. The results are positive only when extensive hepatic damage has occurred. Incidentally, Kimball,³ in an excellent study of the levulose tolerance test, did not use it in cases of catarrhal jaundice.

We employed, therefore, the excretion of intravenously injected bilirubin, originally described by Eilbott and von Bergmann,⁴ as a means of determining the hepatic function in our cases. The work of these authors, as well as that of Harrop and Barron⁵ and our own work,⁶ has led us to the conclusion that this is one of the most sensitive methods of determining the state of hepatic function.

Method.—The method of determining the existence of hepatic involvement by the excretion of intravenously injected bilirubin, together with certain modifications that one of us (L. J. S.⁶) has introduced and which are now employed as a routine in the medical clinic of this hospital, has been described in detail previously. The test, briefly, is performed as follows: A total amount of bilirubin equal to 1 mg. per kilogram of body weight is dissolved in 15 cc. of one-tenth molar solution of sodium carbonate which has been previously brought to the boiling point and then allowed to cool to 80 C. The bilirubin dissolves completely, and a clear iodine-colored solution is obtained. A control sample of oxalated blood is collected in a dry syringe to prevent hemolysis, and with the needle in situ the bilirubin is then injected intravenously. Oxalated samples of blood are obtained from the other arm within five minutes and again four hours after the injection. In the past three years nearly one hundred bilirubin tests have been performed in our clinic, and in no instance have we observed uncomfortable reactions. The concentration of bilirubin in the plasma is determined by means of the Ernst and Förster method.⁷ The plasma is precipitated by redistilled acetone, which is used in different concentrations, depending on the amount of bilirubin in the sample. Thus, with the control and with the samples taken after four hours, 2 cc. of acetone is added to 2 cc. of plasma, while with 1 cc. of the plasma of the specimen taken after five minutes 4 cc. of acetone is used. After the plasma and acetone mixtures are shaken, the samples are centrifugated and filtered directly into a clean, dry colorimeter cup and compared with a standard solution of 1:6,000 potassium dichromate in distilled water. Except during the actual reading in the colorimeter, the acetone solutions of bilirubin must be protected from the light. The bilirubin content of the specimen taken five minutes after the injection minus the bilirubin content of the control sample is considered to contain 100 per cent of the injected pigment. The percentage of bilirubin retained in the sample taken

3. Kimball, Stockton: The Levulose Tolerance Test; a Study of Its Value with Special Reference to Mild and Chronic Diseases of the Liver, *Guy's Hosp. Rep.* **82**:157 (April) 1932.

4. Eilbott, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, *Ztschr. f. klin. Med.* **106**:529, 1927. von Bergmann, G.: Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, *Klin. Wchnschr.* **6**:776, 1927.

5. Harrop, G. A., Jr., and Barron, E. S. G.: The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, *J. Clin. Investigation* **9**:577, 1931.

6. Soffer, L. J.: Bilirubin Excretion as a Test of Liver Function During Normal Pregnancy, *Bull. Johns Hopkins Hosp.* **52**:365 (May) 1933.

7. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blutbilirubins, *Klin. Wchnschr.* **3**:2386, 1924.

after four hours is then calculated, after previous subtraction of the bilirubin contained in the control. The following formulas are employed to determine the amount of bilirubin in the various samples:

$$\text{Control and four hour specimens} = 0.329 \times 2 \text{ (dilution)} \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

$$\text{Five minute specimen} = 0.329 \times 5 \text{ (dilution)} \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

On the basis of previously published control studies⁶ of normal persons, retention of more than 5 per cent of the injected pigment after four hours is considered pathologic.

RESULTS

The results are assembled in the accompanying table. The various examinations other than the tests of hepatic function gave essentially negative results in all instances. In nine of the eleven cases, however, there was a distinctly abnormal response to the bilirubin test. At the time of the study, in four of the nine cases (3, 4, 8 and 10) the patients were symptomless; the remaining five patients complained of indefinite digestive disturbances.

The experience of one of us (Dr. Soffer⁶) with this test in normal control subjects and in patients evidencing conditions in which the liver was not involved coincided with the results of other investigators,⁴ rendering the inclusion of our detailed data on this point unnecessary.

Attention is directed to the degree of retention of bilirubin which indicates residual hepatic involvement in these cases. In nine of the eleven patients, all of whom were regarded as having completely recovered from catarrhal jaundice, the degree of retention of the injected pigment varied from 10.7 to 50 per cent. In six of the nine cases the original attack of jaundice occurred within from three to eighteen years prior to this study. These results are in line with Kalk's⁸ experience, the publication of which appeared while this work was in progress.

COMMENT

Catarrhal or common infective hepatic jaundice has usually been regarded as an innocuous process, since the clinical course in many instances is relatively short and not severe. The apparent well-being of the patient as well as the lack of objective evidence indicating residual hepatic involvement after the jaundice has subsided has served to promote this impression.

The delay in the excretion of intravenously injected bilirubin is, in our opinion, as already noted, one of the most sensitive of present-day means of determining hepatic damage. The fact that such abnormal results were secured in nine of eleven cases in which the attacks of

8. Kalk, Heinz: *Klinische Untersuchungen über die Frage des latenten Leberschadens*, Deutsche med. Wchnschr. 58:1078 (July 8); 1119 (July 15), and 1160 (July 22) 1932.

jaundice occurred from months to many years previous to the study suggests not only that the process is more serious than it is generally regarded but that the hepatic disturbance is in all probability permanent.

Thus, these data give rise to another concept of the disease. Instead of two groups, one in which the hepatobiliary involvement is thought to have completely subsided without residue and a smaller group of rarer cases in which the condition progresses to acute necroses, we now have a third group, which is possibly the largest, in which the chief objective manifestation of the disease is an abnormal delay in the excretion of the injected pigment after four hours. It is conceivable that a number of patients in this group may eventually acquire further hepatic disease, such as cirrhosis.

As will be noted in the table, the severity of an attack bears no relation to the degree of residual hepatic involvement, as determined by this test. This appears to be true with respect to the presence or absence of persisting symptoms and the extent of impaired hepatic function. For instance, the patient in case 4 was symptomless; a friend directed his attention to the yellow discoloration of his eyes. A year later, when the patient was still symptomless and apparently well, the bilirubin retention measured 16.2 per cent. The patients in cases 3 and 8 were symptomless when studied, yet the bilirubin retentions were 10.7 and 19 per cent. The patients in cases 2 and 9, who presented no retention of bilirubin, were asymptomatic. The remaining patients, as already indicated, complained of indefinite discomforts.

SUMMARY

Eleven patients who had had catarrhal jaundice within from three months to eighteen years prior to the investigation were studied by means of the bilirubin excretion test for evidence of residual hepatic damage. It must be emphasized that the original attack was free from such complications as acute yellow atrophy of the liver. Nine of the eleven patients showed degrees of retention of the injected pigment that varied from 10.7 to 50 per cent. Six of the nine patients had had catarrhal jaundice within from three to eighteen years before the investigation.

The degree of residual hepatic damage apparently bears no relationship to the severity of the attack. In view of the response to the test in these cases it is concluded that catarrhal jaundice is not innocuous as is commonly believed, since in a good many instances an impairment of hepatic function occurs which is permanent.

NOTE.—The following inadvertent omission has come to our attention: Jankelson and Gargill (*Bilirubin Liver Function Test*, *New England J. Med.* **204**:547 [March 12] 1931) reported that in chronic cholecystitis the percentages of bilirubin retention were within normal limits.

FACTORS INVOLVED IN THE PRODUCTION OF SKELETAL MUSCLE PAIN

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The cause of muscular pain and the various factors that influence it have been a subject of controversy for many years. Lewis, who has investigated the subject extensively has presented an excellent review of the pertinent literature.¹ More recently Kissin² reviewed the subject from a different angle. While it is now generally accepted that ischemia is the cause of muscular pain, such as occurs in angina pectoris and intermittent claudication, the immediate factors responsible for the pain have not been fully established. The pain which develops in contracting muscles during ischemia might be caused (1) by the direct or indirect action of the lack of oxygen which accompanies ischemia, (2) by the diminution of other materials normally supplied by the arterial blood, (3) by the incomplete mechanical removal of products of muscular metabolism which follows the retardation of the blood flow or (4) by the combined action of several of these factors. Recently, Kissin,² working in this laboratory, showed that generalized anoxemia without ischemia can lead to the development of pain in an exercising muscle. His study, however, did not preclude the possibility that the other factors mentioned which accompany ischemia might also play a significant rôle in the production of pain. The present report deals with the latter problem.

METHOD

The evaluation of the action of the various factors was based on observations obtained during and following exercise under a variety of conditions in a group of ten normal young subjects. Some of the experiments reported in this study are a repetition of those reported by

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1. Lewis, T.: Pain in Muscular Ischemia; Its Relation to Anginal Pain, *Arch. Int. Med.* **49**:713 (May) 1932.

2. Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, *J. Clin. Investigation* **13**:37 (Jan.) 1934.

other observers, notably by Lewis, Pickering and Rothschild³ and by Kissin;² others are new. Most of our observations were made on the leg, whereas previous workers studied the arm.

The arm exercise, unless otherwise stated, consisted of clenching one hand sixty times per minute, in time with a metronome, using maximal effort. During this exercise the subject sat at ease in a chair with the exercising arm supported horizontally on a rest. The leg exercise, unless otherwise stated, consisted of extending one foot against a load sixty times per minute in time with a metronome. The apparatus was arranged to permit the extending foot to lift a weight of 500 Gm. through a distance of 15 cm. This exercise did not require maximal effort. During the exercise the subject reclined on a cot with the lower extremities supported in a horizontal position. A preliminary period of rest of at least ten minutes preceded each period of exercise, unless otherwise stated. Lewis, Pickering and Rothschild³ found that this interval was sufficient to permit full recovery from previous activity.

Complete ischemia was produced in these experiments with a sphygmomanometer cuff inflated to a pressure considerably above the systolic blood pressure. In experiments on the forearm the pressure in the cuff, which was placed on the upper arm, was raised to about 170 mm. of mercury; in the experiments on the leg the pressure in the cuff, which was placed on the lower part of the thigh, was raised to about 200 mm. of mercury.

Circulatory stasis without complete ischemia was produced in these experiments by maintaining a pressure of 80 mm. of mercury in the cuff, a pressure definitely below the systolic and approximately at the level of the diastolic blood pressure of the subjects. The obstruction of the venous outflow produced in this way leads to the accumulation of blood in the limb; and, for a limited time, oxygen is available for the tissues, namely, the oxygen contained in the congested capillaries. The supply of oxygen available to the tissues following venous obstruction is greater than in complete ischemia, since the volume of blood retained in the limb is greater in the former condition and the circulation is not completely stopped. However, the supply of oxygen following venous obstruction is less than normal because of the circulatory stagnation which is produced in the limb.

Various degrees of generalized anoxemia were produced in these experiments by having the subject breathe from a Tissot spirometer containing various mixtures of gases at different times.² The oxygen content of samples of inspired air was determined with the Haldane apparatus.

3. Lewis, T.; Pickering, G. W., and Rothschild, P.: Observations upon Muscular Pain in Intermittent Claudication, *Heart* **15**:359, 1931.

OBSERVATIONS

The observations consisted primarily in determining the time and circumstances under which continuous pain, as described by Lewis,

TABLE 1.—*Effect of a Preliminary Period of Complete Ischemia on the Time of Appearance of Pain During Exercise of the Lower Extremity*

Subject	Pain Produced by		Time When Pain Appeared		Time When Pain Became Unbearable	
	Ischemia for 10 Minutes	Exercise for 10 Minutes	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 10 Minutes After Ischemia, Sec.	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 10 Minutes After Ischemia, Sec.
P. M.	No	No	45 48	23	80 80	33
S. P.	No	No	61	14	103	63
J. P.	No	No	60	15	94	74
B. W.	No	No	148	48	224	138
H. B.	No	No	78	56	130	103
K. J.	No	No	69	45	103	84
R. F.	No	No	80	76	200	141
J. S.	No	No	78	88	183	119
H. K.	No	No	139	126	175	154
L. W.	No	No	85	28	147	85
R. F.*.....	No	No	148	106	238	198

* In this test exercise was at the rate of thirty movements per minute.

TABLE 2.—*Effect of a Preliminary Period of Complete Ischemia on the Time of Appearance of Pain During Exercise of the Upper Extremity*

Subject	Pain Produced by		Time When Pain Appeared		Time When Pain Became Unbearable	
	Ischemia for 5 Minutes	Exercise for 5 Minutes	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 5 Minutes After Ischemia, Sec.	Exercise and Ischemia Started at the Same Time, Sec.	Exercise Started 5 Minutes After Ischemia, Sec.
P. M.	No	No	43 38	12	65 60	38
S. P.	No	No	28 42	8	73 80	22
J. P.	No	No	55	30	70	65
B. W.	No	...	31	20	50	51
H. B.	No	...	39	30	60	50
K. J.	No	...	48	32	70	62
R. F.	No	...	65	43	101	70
J. S.	No	...	64	52	95	65
H. K.	No	...	60	50	80	76
L. W.	No	...	31	16	69	60
R. F.*.....	No	No	58	68	90	100

* In this test exercise was at the rate of thirty movements per minute.

Pickering and Rothschild,³ developed and the time and circumstances under which it disappeared.

It will be seen from the data summarized in tables 1 and 2 for both the leg and the arm that while complete ischemia without exercise, or the

reverse, did not lead to pain, the combination of the two did. This has already been shown by Lewis, Pickering and Rothschild.³ However, contrary to the results of these workers, we found that when the complete ischemia was started five or ten minutes before the exercise, the time required for the onset of mild and unbearable pain was considerably

TABLE 3.—*Effect of Continuing Complete Ischemia on Appearance of Pain When Exercise Is Stopped Before Pain Develops*

Procedure	Control Exercise and Ischemia Started Simultane- ously, Sec.	Ischemia Continuous, but Exercise Stopped After			Subject
		30 Sec.	26 Sec.	16 Sec.	
Onset of pain after start of ischemia.....	35 30	131	130	210 190	P. M. (upper extremity)
Pain became unbearable after start of ischemia	52 45	200	185	610 625	
Onset of pain after start of ischemia.....	31 32	28 Sec. 130 140	17 Sec. 320 340		S. P. (upper extremity)
Pain became unbearable after start of ischemia	55 62	340 354	*		
Onset of pain after start of ischemia.....	39 42	35 Sec. 285 260			B. W. (upper extremity)
Pain became unbearable after start of ischemia	60 63	*			
Onset of pain after start of ischemia.....	80 100	75 Sec. 512			R. F. (upper extremity)
Pain became unbearable after start of ischemia	100 125	*			
Onset of pain after start of ischemia.....	45	40 Sec. 185			P. M. (lower extremity)
Pain became unbearable after start of ischemia	85	*			
Onset of pain after start of ischemia.....	43	40 Sec. 301			S. P. (lower extremity)
Pain became unbearable after start of ischemia	107	*			

* Pain increased but did not become unbearable.

shortened in practically all our experiments. In the leg the abbreviation of the two intervals was marked in most instances.

The action of complete ischemia in the production of pain in the arm was shown on repeating another type of experiment of Lewis and his co-workers,³ which consisted in stopping the exercise short of the point at which pain would have appeared, the ischemia being maintained. The results summarized in table 3 show that in our experiments continuation of the ischemia after stopping the exercise led to the development of pain, contrary to the findings of Lewis and his co-workers. The time of its appearance was considerably delayed, in many instances

beyond five minutes. In some experiments the pain did not increase sufficiently to become unbearable during the fifteen to twenty minute period of ischemia after the cessation of exercise. Ischemia was not continued longer than this because numbness and tingling became noticeable. The interval before the onset of pain was least when the end of the period of exercise was closest to the time at which pain appeared in the preliminary experiments. When the exercise was stopped earlier, the delayed pain often started so insidiously that the exact time of its onset was not always sharply defined, the subject being able to state only that the pain had begun in the previous thirty to sixty seconds.

TABLE 4.—*Effect of Generalized Anoxemia and Circulatory Stasis on Appearance of Pain During Exercise of the Lower Extremity (Subject S. P.)*

Test Done		Stasis Present or Absent	Oxygen Level in Inspired Air,* Volume per Cent	Pain Appearing After Onset of Exercise, Time in Seconds	Pain Becoming Unbearable After Onset of Exercise, Time in Seconds
Day	Order				
6	15	No	21.0	No pain in 600 seconds	
1	1	No	14.5	No pain in 600 seconds	
1	3	No	13.6	No pain in 600 seconds	
2	4	No	11.2	No pain in 540 seconds	
3	7	No	10.1	No pain in 480 seconds	
4	10	No	7.6	No pain in 720 seconds	
6	14	Yes	21.0	No pain in 600 seconds	
1	2	Yes	15.4	No pain in 600 seconds	
4	11	Yes	14.8	332	964
4	9	Yes	14.1	338	756
2	5	Yes	11.8	219	703
3	6	Yes	10.8	195	630
3	8	Yes	9.3	153	382
5	12	Yes	8.1	54	168
6	13	Ischemia present (control)	21.0	34	86

* In all cases the exercise was begun two minutes after anoxemia was started.

In the only subject tested generalized anoxemia alone did not lead to the development of pain when the lower limb was exercised for ten minutes (in the same way as in the complete experiments on ischemia), even when the level for oxygen in the inspired air was as low as 7.6 per cent by volume (table 4). Pain did appear, however, and become unbearable when the generalized anoxemia was associated with circulatory stasis. As shown in table 4, the pain appeared when the oxygen content of the inspired air was reduced to 14.8 per cent by volume. The periods of exercise necessary to cause pain and to make it unbearable shortened progressively as the degree of generalized anoxemia was increased. These intervals of time, however, were longer than in complete ischemia, even when the level for oxygen in the inspired air was 8.1 per cent by volume (table 4). The interval between the first appearance of pain and the time when it became unbearable also shortened as the degree of anoxemia was increased.

The rôle of circulatory stasis was shown in another group of experiments on the leg, in which the periods of exercise required for pain to appear and to become unbearable were determined in a preliminary period of exercise under total ischemia; these intervals of time were compared with those of a second period of exercise and ischemia carried out after a short interval during which the total ischemia was temporarily abated and one of the following four conditions was substituted: (1) circulatory stasis and exercise, (2) exercise alone, (3) circulatory stasis alone, (4) a state of rest, with no stasis or exercise. The results are summarized in table 5.⁴ When the interval between the two ischemic periods was short, as in L. W., the pain appeared sooner in the second period than in the first, regardless of whether or not exercise or stasis

TABLE 5.—*Effect of Temporary Relief of Ischemia on the Time Pain Reappears During a Second Ischemic Period (Lower Extremity)*

Sub- ject	Onset of Pain					Pain Becoming Unbearable					Dura- tion of Inter- lude, Sec.
	First Period of Exercise and Ischemia, Sec.	Second Period of Exercise and Ischemia After Interlude with				First Period of Exercise and Ischemia, Sec.	Second Period of Exercise and Ischemia After Interlude with				
		Stasis and Exer- cise, Sec.	Stasis Alone, Sec.	Exer- cise Alone, Sec.	No Stasis or Exer- cise, Sec.		Stasis and Exer- cise, Sec.	Stasis Alone, Sec.	Exer- cise Alone, Sec.	No Stasis or Exer- cise, Sec.	
S. P.	65 ± 15	27	23	50	80	127 ± 15	71	71	113	155	185
P. M.	44 ± 8	27	46	40	45	78 ± 12	55	62	69	71	150
R. F.	94 ± 20	35	69	23	126	158 ± 25	105	134	45	176	180
L. W.	75 ± 5	40	23	13	46	125 ± 18	85	67	46	98	45

was present during the interval between them. When a longer period of rest was allowed between the two ischemic periods the onset of mild and unbearable pain did not occur earlier in the second period of exercise and ischemia than in the first. However, when the exercise, the stasis or both were maintained during this longer interval, mild and unbearable pain appeared earlier in the second period of exercise and ischemia than in the first. In the case of S. P. a decrease of these intervals of time in the second period of ischemia and exercise occurred when stasis was continued in the interlude; maintaining exercise alone during the interlude had no such effect. In the case of R. F., however, the reverse was true; and in the case of P. M. this abbreviation in the second period of ischemia and exercise occurred only when both the exercise and the stasis were maintained in the interlude.

4. In this group of experiments the control is the average of four determinations. It will be seen that the intervals of time required for the development of mild and unbearable pain are more variable than those reported by Lewis, Pickering and Rothschild³ and those found in our other determinations.

In S. P., after unbearable pain had developed while exercising during general anoxemia and circulatory stasis, a short interval of rest, without abating the general anoxemia and circulatory stasis, was followed in every trial by a shortening of the intervals required to produce mild or unbearable pain in the second period of exercise, as the results assembled in table 6 show.⁵ In this subject a similar period of rest, without anoxemia or stasis, was not followed by such an abbreviation of the

TABLE 6.—*Effect of Temporary Interlude of Rest with Generalized Anoxemia and Circulatory Stasis Maintained on the Time Pain Reappears (Lower Extremity, Subject S. P.)*

Onset of pain				
First period of exercise, seconds.....	332	219	195	158
Second period of exercise, seconds.....	228	70	28	136
Time at which pain became unbearable				
First period of exercise, seconds.....	964	793	630	382
Second period of exercise, seconds.....	425	170	119	284
Oxygen in inspired air, per cent by volume				
First period of exercise.....	14.1	11.8	10.8	9.3
Second period of exercise.....	13.8	16.3	7.9	8.5
Duration of interlude, seconds.....		150		250

TABLE 7.—*Effect of Ischemia, Stasis and Generalized Anoxemia on the Disappearance of Pain Produced by Exercise of the Lower Extremity*

Subject	Ischemia Relieved, Exercise Stopped, No Stasis, Seconds	Ischemia Relieved, Exercise Persists, No Stasis, Seconds	Ischemia Relieved, Exercise Stopped, Stasis Persists, Seconds	Ischemia Relieved, Exercise and Stasis Persists, Seconds	Ischemia Persists, Exercise Stopped	Generalized Anoxemia and Stasis Persist, Exercise Stopped, Seconds	Generalized Anoxemia and Exercise Persist, Stasis Relieved, Seconds
S. P.	5 to 7	10 to 14	14	13	Pain does not disappear, but continues unabated or even increases	149 (16.3%)* 146 (14.1%)* 116 (9.2%)* 241 (7.9%)*	4 (16.3%)* 38 (8.5%)* 54 (8.1%)*
P. M.	5 to 10	4	10	10			
R. F.	5 to 19	7	4 to 15				
L. W.	6 to 22	10	5 to 31	5			

* Oxygen level in the inspired air, per cent by volume.

second period of exercise even though the exercise was carried out during complete ischemia (table 5).

The time required for pain to disappear under various conditions was also analyzed, and the data on four subjects are assembled in table 7. No essential difference was found in the time taken for pain to disappear, provided the complete ischemia was relieved, regardless of whether or not circulatory stasis or exercise was continued. On the other hand, so long

5. The more marked shortening in the third trial (third column of table 6) is due in part to the lowered oxygen content in the inspired air when the second period of exercise was carried out, which followed the necessarily rapid refilling of the spirometer in the interval between periods of exercise.

as the ischemia was maintained pain was found to persist unabated or even to increase after the exercise was stopped.⁶ Furthermore, the time taken for pain to disappear was found to be prolonged when generalized anoxemia and circulatory stasis were maintained after the cessation of exercise. The time taken for pain to disappear, however, was prolonged only slightly if exercise and general anoxemia were maintained but circulatory stasis was relieved.

COMMENT

Our results, with the few exceptions to be discussed later, are in accordance with the observations of Zak,⁷ MacWilliam and Webster,⁸ Lewis, Pickering and Rothschild,³ Reid⁹ and Kissin.²

They confirm previous observations that continuous pain is brought on after a short interval (from one to two minutes) in the exercising muscle when complete ischemia is produced, and that the pain becomes unbearable if exercise is continued. However, our results show that exercise with circulatory stasis but without anoxemia fails to produce pain in the leg in ten minutes under the conditions of our experiments, although in one subject (S. P.) on one occasion exercise with circulatory stasis led to the development of pain after sixteen minutes and ten seconds, just before tingling began. The pain produced by exercise of both the arm and the leg during complete ischemia disappears after a short lag whenever the complete ischemia is relieved, even if the exercise is continued and circulatory stasis is maintained (table 7). These observations seem to indicate that anoxemia must be severe to become an important element in the production of pain in an exercising muscle during ischemia (Kissin²).

In our experiments general anoxemia alone, however, failed to produce pain in ten minutes in the exercising muscles of the leg unless associated with circulatory stasis (table 4). This apparent contradiction of Kissin's observations probably depends on the different type of exercise used in the two investigations. Extension of the foot at the ankle, which was carried out in the present study, is a movement constantly employed in walking, so that training may tend to make compen-

6. While the exercise was continued until the pain became unbearable and forced the subject to stop the exercise, nevertheless in some, pain became even more marked after the exercise had ceased but while the ischemia was maintained.

7. Zak, E.: Ueber den Gefäßkrampf bei intermittierendem Hinken und über gewisse Kapillomotorische Erscheinungen, *Wien. Arch. f. inn. Med.* **2**:404, 1921.

8. MacWilliam, J. A., and Webster, W. J.: Some Applications of Physiology to Medicine: I. Sensory Phenomena Associated with Defective Blood Supply to Working Muscles, *Brit. M. J.* **1**:51, 1923.

9. Reid, C.: Experimental Ischemia: Sensory Phenomena, Fibrillary Twitchings, and Effects on Pulse, Respiration, and Blood-Pressure, *Quart. J. Exper. Physiol.* **21**:243, 1931.

satory adjustment easier than in the less constantly employed gripping movement of the hand used by Kissin. The conditions of the leg exercise could not conveniently be made more strenuous. It is not easy to perform the leg exercise faster than sixty times a minute, nor is it convenient to load the exercising leg with weights approaching those lifted by the foot in walking. Furthermore, the degree of general anoxemia that can be employed is set by the general reaction of the subject. Our observations, however, serve to emphasize the fact that circulatory stasis is an important factor in the production of pain during ischemia. Circulatory stasis can be considered as acting to supplement the action of anoxemia. The important rôle of stasis is also seen in the experiments assembled in tables 5 and 6, in which it is shown that the presence of stasis in the interval between the first and second periods of exercise and ischemia (also the periods of exercise and anoxemia) had a definite tendency to abbreviate the time of onset of mild and of unbearable pain.

It appears, therefore, that both stasis and anoxemia are important in determining the appearance of pain during exercise. They also have an important influence on the disappearance of pain. When both stasis and anoxemia are maintained, pain abates more slowly than when they are relieved (table 7). If the anoxemia and stasis are at a maximum, as in complete ischemia, pain continues unabated after the cessation of the exercise. Anoxemia has a greater effect in prolonging pain than stasis has, since without stopping the exercise, relieving the latter but continuing the former prolongs the time before pain disappears, whereas the relief of the former but not of the latter has little effect in prolonging the time before pain disappears (table 7).

A repetition of some of the experiments of Lewis, Pickering and Rothschild³ with complete ischemia yielded results different from those which they obtained. We found that a preliminary period of ischemia definitely shortens the duration of exercise necessary to produce mild and unbearable pain in both the arm and the leg (tables 1 and 2). Lewis and his co-workers reported that a preliminary period of ischemia had no such effect in the arm. Furthermore, we found that continuing the ischemia after stopping the exercise short of the point at which pain appears led to the development of pain in the arm (table 3), whereas Lewis and his co-workers reported that under such circumstances pain did not develop. If our results are correct, there is no necessity to assume, as Lewis has done, that the stimulated pain nerve endings are in the tissues surrounding the muscle and not in the muscles themselves.

Our results suggest that the only difference between the metabolism of rest and that of exercise is one of degree. A rough calculation would place the ratio between the two somewhere close to 1:20 to 1:80 in our experiments, which is the magnitude generally accepted on the basis

of thermodynamic studies (Hill¹⁰). Our observations are in accord with the finding of Lewis and his co-workers³ that exercise without ischemia followed immediately by ischemia without exercise leads to pain, a result which appears paradoxical in view of the other results reported by them. We interpret this observation of theirs as follows: The preliminary period of exercise built up the concentration of the pain-producing substance which was augmented by the metabolism of the resting ischemic limb sufficiently to raise the pain-producing substance above the threshold for pain. The hypothesis of diffusion of the pain-producing substance which Lewis used to explain his results is, as our observations show, at present unnecessary. In view of our findings, the pain-producing substance could act just as readily within the muscle.

Our results further incline us to the view held by previous observers that the pain-producing factor is a chemical substance. However, our results indicate that this is formed during muscular metabolism, not only during exercise but also while the muscle is at rest. The rate of formation is slow while the muscle is at rest but is greatly accelerated during exercise. This substance is diffusible into the blood stream and can be carried away, but it can also be changed locally, in the presence of an adequate amount of oxygen, into substances which do not cause pain. Interference with either its mechanical removal by the circulation or its local oxidation, or both, will lead to the accumulation of the pain-producing substance in the muscles. If the interference with these two factors is sufficiently great in relation to the muscular activity of the part, then the concentration of the pain-producing substance can become great enough to exceed the threshold necessary to stimulate the pain nerve endings.

Our experiments do not rule out the possibility that the threshold of the pain nerve endings may be variable. Thus it is not at all unlikely that one of the actions of ischemia, circulatory stasis, anoxemia or exercise itself might be to enhance the susceptibility of the pain nerve end-organs to the pain-producing substance, thus lowering the threshold to pain. It is known (Lewis and co-workers¹¹) that ischemia continued for forty minutes has the reverse action; namely, it deadens sensations of pain in the ischemic limb.¹²

10. Hill, A. V.: *Muscular Movement in Man*, New York, McGraw-Hill Book Company, Inc., 1927.

11. Lewis, T.; Pickering, G. W., and Rothschild, P.: *Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb, Including Notes on a Form of Tingling*, *Heart* **16**:1, 1931.

12. The variability in the amount of exercise necessary to lead to mild and to unbearable pain, which amounted to from ten to twenty seconds from day to day, may be due in part to a variability in the sensitivity of the pain nerve endings.

Our results show clearly that there is a prepain stage in which the pain-producing substance is above normal but below the pain-producing threshold. It follows, therefore, that the absence of pain, or its disappearance, does not imply full restoration of the muscle to normal as far as the pain-producing substance is concerned, but merely indicates a sufficient diminution in the amount of the pain-producing substance to reduce its concentration below the threshold for pain. This is shown strikingly by the variability of the duration of exercise necessary to produce mild and unbearable pain after different preliminary conditions. As indicated by our results improvement in the condition of the muscle, in the sense of delaying pain on exertion, would be attainable by decreasing the work of the muscle, or its tone, by increasing the supply of oxygen and by improving the circulation locally.

This analysis may be applicable to the mechanism for the production of pain in intermittent claudication and angina pectoris.

SUMMARY

Our results show that the immediate cause of continuous muscular pain, such as occurs when an ischemic muscle is exercised, is not produced by a single mechanism but that muscular activity, anoxemia, circulatory stasis and possibly other processes contribute to its production.

BLOOD CHOLESTEROL AND HYPOMETABOLISM

SUPRARENAL AND PITUITARY DEFICIENCY, OBESITY AND MISCELLANEOUS CONDITIONS

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Low metabolic rates are found in conditions in which the thyroid gland does not appear to be involved. It was shown in preceding papers¹ that hypercholesteremia was characteristic of thyroid deficiency regardless of observed metabolic rates. This report therefore deals with observations on the blood cholesterol in other conditions in which hypometabolism was encountered.

In evaluating the basal metabolism test, it is important to remember two things: (1) that it is probably impossible to obtain true basal metabolic rates in some persons because of nervousness or lack of cooperation, and (2) that repetition of the basal metabolism test and keeping the subject in the hospital overnight will tend to give lower readings than are obtained when these procedures are not carried out. In other words, the metabolism is subject to influences which are often beyond the examiner's control. Thus, while groups may show various trends, individual cases may occasionally show no correlation between clinical phenomena and the basal metabolic rate observed.

Is the rate of metabolism dependent on the activity of one endocrine gland? In general practice the basal metabolism is considered as being so closely linked with the thyroid gland that variation in one is considered to indicate a direct or indirect change in the other. If hypercholesteremia is an invariable accompaniment of thyroid deficiency, hypometabolism without hypercholesteremia is dependent on factors other than thyroid.

Three definite clinical conditions of endocrine origin which may lower the metabolism are: thyroid deficiency, or myxedema and cretinism; suprarenal deficiency, or Addison's disease, and hypophyseal

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1. (a) Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: I. Analysis of Findings in Toxic and in Nontoxic Goiter Before Treatment, *Arch. Int. Med.* **51**:22 (Jan.) 1933; (b) Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, *ibid.* **52**:86 (July) 1933; (c) Blood Cholesterol in Thyroid Disease: III. Myxedema and Hypercholesteremia, *ibid.* **53**:762 (May) 1934.

deficiency associated with pituitary chromophobe tumors.² In connection with two of these glands, elevated metabolisms are found when the opposite clinical picture is present, i. e., hyperthyroidism and acromegaly, and in the case of the suprarenal glands, overactivity of the medulla at least will raise the metabolic rate.

There are certain clinical phenomena occurring in connection with the interrelationship of these glands which are well known and which will be mentioned here only as they relate to the blood cholesterol and hypometabolism.

In regard to the relationship between the suprarenal and the thyroid glands, Crile³ stated the belief that it would be impossible for exophthalmic goiter to develop in a patient with Addison's disease. The question is, therefore, Which is more important in the production of the high basal rates in this disease, the thyroid or the suprarenal glands? Epinephrine excites the patient with hyperthyroidism, but has little effect on the myxedematous patient.³ Long-standing exophthalmic goiter may produce asthenia and pigmentation, and the basal metabolic rate may not be significantly elevated. This suggests that the thyroid activates the suprarenal glands, which in turn produce the marked nervous symptoms of that disease, and when this nervous energy has been exhausted, the aforementioned type of apathetic hyperthyroidism results. In Addison's disease, on the other hand, if the low metabolic rate were due to an indirect atrophy of the thyroid and thus to thyroid deficiency, administration of thyroid would be helpful; as a matter of fact, it is the consensus that treatment with thyroid is dangerous. If hypometabolism in myxedema likewise were due to an indirect deficiency of the suprarenal glands, cortical extract or epinephrine might be helpful, but it is doubtful if these preparations would effect a cure. That the thyroid is not deficient in Addison's disease is further suggested by the absence of hypercholesteremia. In one case of Addison's disease in which I gave thyroid experimentally, a certain amount of stimulation, the drop in the cholesterol and in the weight and the rise in the pulse rate without apparent influence on the metabolism were suggestive evidence that the thyroid had an effect. It is also probably true that these changes would have come about during the natural progression of the disease. Administration of extract of suprarenal cortex intravenously raised the basal metabolic rate in three days (table 1).

2. Dr. E. P. McCullagh has called my attention to the finding of hypercholesteremia in hypogonadism (McCullagh, E. P.; McCullagh, D. R., and Hicken, N. F.: *Diagnosis and Treatment of Hypogonadism in the Male*, Endocrinology **17**:49 [Feb.] 1933).

3. Crile, G. W., and others: *Diseases of the Thyroid Gland*, Philadelphia, W. B. Saunders Company, 1932, p. 419.

Injections of thyrotropic anterior pituitary extracts have been shown to cause hypertrophy of the thyroid and suprarenal glands, whereas removal of the hypophysis has been followed by atrophy of these organs.⁴ So far as I can determine, studies of the blood cholesterol have not been made in these experiments. In five cases of proved⁵ pituitary (chromophobe) adenomas with low metabolic rates, the blood cholesterol was not over 200 mg. per hundred cubic centimeters in four male patients, but it was above this value (229 mg.) in the one female

TABLE 1.—*Patients with Addison's Disease*

Serial Number	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	
30519	55	M	-29	63	181	+1	153	First observations
			-26	88	165	135	After two weeks on desiccated thyroid, 2 grains a day, patient warmer, more active, less sleepy after extract of suprarenal cortex given intravenously
			-2	80	165	
30625	53	F	-27	88	106	-21	185	First observation
			-14	88	107	189	Six days after extract of suprarenal cortex; death later; autopsy

TABLE 2.—*Patients with Pituitary Chromophobe Adenomas*

Serial Number	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	
30671	29	M	-30	62	93	-30	133	Before operation
31869	37	F	-21	70	119	-8	243	Before operation
			-29	64	114	229	After operation
31604	26	M	-18	64	232	+30	116	Before operation
			-34	76	223	110	Three weeks after operation
			-27	66	225	152	Five weeks after operation
30876	55	M	-33	58	172	+9	205	Before operation
32274	45	M	-37	70	124	-20	191	Before operation

(table 2). In none of these patients were there clinical indications of myxedema, a finding which suggests, I think, that the low metabolic rate is not due to a secondary thyroid atrophy. The absence of hypercholesteremia further substantiates this. Collip demonstrated a hormone from the anterior pituitary body which raised the metabolism, yet a rise in the metabolism may take place regardless of hyperplasia in the thyroid. Hyperplasia may indicate merely the effect of the

4. Anderson, E. M., and Collip, J. B.: Thyrotropic Hormone of Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* 3:680 (Feb.) 1933.

5. These patients were operated on in the neurosurgical section of the clinic by Dr. Gilbert Horrax.

pituitary hormone and not the cause of the elevated metabolism. Hyperplasia of the thyroid in such instances may indicate an attempt to supply the increased demands on the thyroid as the result of increased metabolism instigated by the injection of the anterior pituitary hormone. Clinically, this might be exemplified by active acromegaly, or by the enlargement of the thyroid during the menstrual cycle, at which time, too, the pituitary gland is probably more active than usual. Likewise, the atrophy of the thyroid following hypophysectomy may point to diminished demands on the thyroid as the result of a scaling down of the metabolism, there being no deficiency of thyroxine in relation to bodily needs. Simonds and Helper,⁶ found atrophy of the thyroid as

TABLE 3.—*Patients with Obesity*

Serial Number	Sex	Age	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Choles- terol, Mg. per 100 Cc.	Deviation in Weight, per Cent
26747.....	F	32	206
26643.....	F	46	+24	84	200	206	+35
19493.....	F	43	-4	78	188	141	+15
20534.....	F	14	-19	78	148	156	+28
26926.....	F	10	-24	..	96	179
19492.....	F	16	-23	70	200	137	+56
21812.....	F	20	-15	67	195	126	+39
20539.....	F	30	-14	74	175	183	+37
D.....	F	33	-14	80	161	198	+28
27166.....	F	46	-10	56	196	234	+28
21102.....	F	47	-11	78	174	183	+15
24995.....	F	54	-16	74	163	132	+16
24698.....	F	55	-15	75	187	183	+35
21140.....	F	60	-11	76	177	170	+25
26726.....	F	42	-7	76	184	248	+42
26242.....	M	13	-15	80	...	174
24951.....	F	39	-1	80	161	136	+20
21224.....	F	45	-1	66	149	111	+8
McC.....	F	19	-4	76	230	185
17573.....	F	45	-1	72	194	176	+43
20997.....	F	44	188
26241.....	F	35	-7	86	194	219	+49
30724.....	F	26	-18	66	152	158
26747.....	F	30	169	204
29578.....	F	28	180

a result of feeding thyroid to dogs. It might be said in this case that, in view of a plentiful external supply of thyroxine, the thyroid atrophies because there is no demand for its secretion. However, when the external supply is cut off, the output of thyroid is insufficient to meet the normal metabolic needs, and hypercholesteremia results. An analogy might be found in the development of a deficiency of insulin after dieting when on the resumption of a normal intake of carbohydrates a decreased tolerance is found.

OBSESITY

Determinations of the blood cholesterol were made in twenty-one cases of obesity (table 3). Basal metabolic rates were obtained in

6. Simonds, J. P., and Helper, O. E.: Fat Tolerance in Experimental Hyperthyroidism, J. A. M. A. 98:283 (Jan. 23) 1932.

fifteen cases. No attempt was made to place an endocrine label on these cases. Of these patients all except one showed a low metabolic rate, yet the cholesterol values with one exception were within the normal range. The average cholesterol value for the group was 171 mg., and the average metabolism was -13 per cent. These findings are additional evidence that most cases of obesity with low metabolic rates are not of thyroid origin.

That most obesity results from thyroid deficiency is now universally considered as unlikely, yet the conception that a patient with myxedema is always obese still holds fast in the minds of many persons. In forty-five cases of nonoperative myxedema which were observed, 22 per cent of the patients were underweight, 11 per cent of normal weight and 66 per cent overweight. This undoubtedly explains why in so many cases of obesity the question of thyroid deficiency is raised. Some patients with obesity do well when thyroid extract is administered, and others do not. Deficiency in the output of thyroid may increase the weight in one who is naturally obese, but it does not cause obesity in a patient who is usually underweight.

Obesity may not infrequently be associated with thyroid failure and, as pointed out before,^{1c} evidence of myxedema may be conceded. There thus would appear to be some logic in carefully considering thyroid deficiency in obesity, and this can be more thoroughly accomplished not only by questioning the patient carefully to elicit some of the more characteristic symptoms of thyroid failure and by obtaining the basal metabolic rate, but also by determining the blood cholesterol. This has been demonstrated to my satisfaction time and again, not only in a few cases following operation on the thyroid, but also in cases of obesity and normal or low metabolic rates.

MISCELLANEOUS CONDITIONS

From the data collected, fifty-six patients with normal thyroid glands on palpation, whose basal metabolic rates were below -9 per cent, were selected. These cases cover a variety of clinical conditions (table 4). For purposes of investigation, desiccated thyroid was prescribed in about one half of the cases, without benefit in most instances. The dose was usually from 1 to 2 grains (0.065 to 0.13 Gm.) of desiccated thyroid a day. This striking failure of thyroid substance to benefit the patient might be attributed to biased judgment. The opinion as to whether or not a given medication is beneficial is often formed from preconceived notions as to its efficacy and not from a critical analysis of the results actually obtained. The mere statement of the patients that they felt better as a result of a prescribed treatment is not always trustworthy evidence of physical benefit. Even though a physical change can be dem-

TABLE 4.—Patients with Hypometabolism

Serial No.	Age	Sex	Basal Metabolic Rate, per Cent	Pulse Rate	Weight, Lbs.	Deviation in Weight, per Cent	Cholesterol, Mg. per 100 Cc.	Took Thyroid Extract†	Diagnosis and Comment
26926	10	F	-24	96	145	+100	179	..	Obesity
26292	13	M	-15	80	174	+	Obesity
22819	13	F	-22	58	97	-18	128	+	Malnutrition (later gained 30 pounds; basal metabolic rate still -20)
21442	14	F	-17	84	147	+27	133	..	Chorea
20384	14	F	-19	78	148	+28	156	+	Obesity
15632	15	F	-15	64	135	+10	135	..	Fatigue neurosis
19492	16	F	-23	70	200	+56	137	+	Obesity
24880	17	F	-12	78	128	0	169	+	No disease
21952	18	F	-28	66	81	-35	177	+	Schizophrenia (malnutrition)
24347	19	F	-19	60	144	+3	167	+	Fatigue
21312	20	F	-15	67	195	+39	126	+	Obesity
21252	20	F	-16	..	121	136	..	Amenorrhea
23672	21	M	-15	51	97	-31	151	..	Malnutrition; depression
22142	23	F	-19	76	106	-13	200	..	Manic-depressive psychosis
24347	27	F	-22	52	140	+6	185	+	Trophedema
23443	28	F	-10	76	106	-13	184	..	Chronic salpingitis
20387	29	F	-11	86	138	+10	214	+	No disease
20339	30	F	-14	74	175	+37	183	+	Obesity
22549	31	F	-11	62	148	+10	151	..	Muscle-bound feet
21905	31	F	-21	64	143	-3	192	..	Cushing's syndrome (proved)
25035	32	M	-17	62	168	+6	198	..	No disease
23666	32	F	-22	68	172	+38	219	+	Polyglandular syndrome; obesity
23056	32	F	-17	64	120	-11	156	+	Anemia; fibroid uterus
D.	33	F	-14	80	161	+28	198	+	Obesity
24024	33	F	-17	72	145	+15	219	+	Chronic arthritis, spine
22686	37	F	-17	68	86	-30	130	..	Psychoneurosis
23470	38	F	-18	86	109	-20	171	+	No disease
21838	38	F	-22	68	159	+16	176	+	Anxiety neurosis; sleepy and tired
24886	40	F	-11	74	122	-4	198	..	Cholecystitis, chronic
3866	40	F	-25	68	129	-2	154	+	Constipation; nervous; "can't take it"
M	14	F	-30	70	116	-17	154	..	Psychoneurosis
23548	44	F	-15	86	145	-4	250	..	Psychoneurosis; syphilis; allergy
2212	44	F	-20	75	133	±0	180	..	Eczema
26883	45	F	-22	80	126	-12	197	..	Constipation
27166	46	F	-10	56	196	+28	234	+	Obesity
19184	46	F	-13	66	140	+5	153	+	Sleepy; fatigued
21851	47	F	-24	64	146	-9	181	..	Hypertension
20998	47	F	-26	56	177	+1	195	..	Chronic hypertrophic arthritis
27555	47	F	-13	74	196	+41	229	+	Neurosis; obesity
25842	47	F	-14	78	146	+7	205	..	Chronic arthritis
21102	47	F	-11	78	174	+15	183	..	Obesity
27470	48	F	-22	72	178	+26	229	..	Menopause; obesity
27702	49	F	-20	72	140	+4	171	+	Hypochromic anemia; felt better on thyroid
28046	49	F	-21	62	137	+4	147	..	Hypotension; fatigue
20790	50	F	-18	60	150	-4	167	+	Migraine; felt better on thyroid, ½ grain daily
21622	51	F	-13	70	151	+2	202	..	Aching legs
23390	51	F	-11	72	143	-2	167	?	Ascariasis; took thyroid 5 years before for headache, with improvement
24995	54	F	-16	74	163	+16	133	..	Obesity; chronic arthritis
23981	54	F	-10	85	130	-6	185	?	Arteriosclerosis
24863	55	F	-18	68	117	-13	208	..	Multiple sclerosis
17295	55	F	-14	80	173	+22	184	..	Paget's disease
24698	55	F	-15	75	187	+35	183	+	Obesity; hypertension
29224	56	F	-11	72	107	-19	205	..	Chronic atrophic arthritis
21149	60	F	-11	76	177	+25	170	..	Obesity; arthritis
28011	67	F	-18	48	183	+30	167	+	Senile psychosis

† Thyroid appeared to be helpful in only two cases, 20790 and 27702.

onstrated, it does not follow that there existed a specific lack of the particular substance administered. There is little doubt that many patients obtain a real benefit from the use of thyroid extract whether they have a low metabolic rate or not, so that in a sense they may be said to respond to treatment. It is a characteristic feature of most patients with exophthalmic goiter, when the disease is not too severe, to feel well, eat well and sleep well; that this is due to increased secretion of thyroid and the resultant increased metabolic processes cannot, I believe, be denied. I have seen a few patients cured of moderate hyperthyroidism and its annoying symptoms of palpitation, dyspnea, sweating, easy fatigue and the like, who have missed, I am sure, the feeling of well-being at rest which was present before operation. This stimulus undoubtedly can be used to advantage in certain persons, regardless of the level of the basal metabolic rate. It is probable that low basal metabolic rates are found as frequently in normal persons as in the patients seen in the office. But when a low basal metabolic rate is discovered in a more or less exhaustive survey for diagnosis, it may be regarded as evidence of hypothyroidism; thyroid is then prescribed in some form, the patient feels better, and the conclusion is thyroid deficiency. This is not rational but empirical therapy and leads only to confusion in the field of endocrinology.

Thyroid extract has been used in the treatment of chronic arthritis, and low basal metabolic rates are occasionally found in these cases. Its use may originally have suggested itself as the result of some striking case of myxedema in which symptoms of the joint were predominant. The rationality of its use now lies partly in the increased flow of blood associated with mild, induced hyperthyroidism. I can recall only two cases of myxedema in which symptoms of the joint were given as the chief complaint, although it is frequently a secondary complaint. In fifteen cases of chronic hypertrophic arthritis, the cholesterol values were above the normal range in two patients, one of whom had a basal metabolic rate of -2 per cent; in the other, the basal metabolic rate was not determined. I have not observed definite benefit from the use of desiccated thyroid in arthritic cases.

CONCLUSIONS

1. Hypometabolism associated with known suprarenal or pituitary insufficiency was not accompanied by hypercholesteremia in this series.
2. Obesity was usually accompanied by relative hypometabolism and a normal blood cholesterol. If hypercholesteremia is found, there may be an associated or concealed myxedema.
3. Hypometabolism found in miscellaneous clinical conditions is probably not due to thyroid failure in view of the absence of hypercholesteremia.

MALIGNANT HYPERTENSION: THE HISTOLOGIC CHANGES IN THE KIDNEYS

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The relationship of arterial disease to disease of the kidneys is far from accurately settled.¹ As a contribution to the subject I determined, in twenty-seven cases, the size and the weight of the kidneys and the ratio of the wall to the lumen of the renal arterioles in relation to histologic renal changes. So far as I know, this is the largest series of cases in which both a clinical diagnosis of malignant hypertension and a histologic study of the tissue obtained at necropsy have been made.

Consciously, or without elaborately detailed distinction, most physicians have considered various grades of severity in cases of arterial hypertension. Perhaps Volhard and Fahr,² in 1914, were most definite in this regard. For them there was a *bösartige* type distinct from a milder one. Later Fahr³ used the term malignant nephrosclerosis to indicate the picture presented by the kidneys in a severe type of disease. In 1924, Keith and Wagener⁴ separated and identified a group of cases more definitely, establishing a clinical basis for diagnosis. This consisted in a sustained, elevated blood pressure combined with neuroretinitis, but without appreciable anemia or impairment of the renal function until the later stages of the disease. Fuller elaboration of this concept is contained in more recent reports by Keith, Wagener

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1. Moschowitz, Eli: Hypertension: Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology. *Am. J. M. Sc.* **158**:668 (Nov.) 1919.

2. Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

3. Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, *Deutsches Arch. f. klin. Med.* **134**:366, 1920.

4. Keith, N. M., and Wagener, H. P.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *Arch. Int. Med.* **34**:374 (Sept.) 1924.

and Kernohan.⁵ The short duration of symptoms, the tendency to affect comparatively young persons and the maintenance of good renal function until a late stage were predominant features in the majority of cases. It is impossible at present to indicate a single test of renal function which may not be criticized for one reason or another. Hence, it is difficult, even when many methods of examination are used, to determine precisely early stages of renal injury. Major⁶ stressed this feature in particular and suggested additional methods.

The reports of cases given at the end of this paper have been abbreviated from histories in the files of the Mayo Clinic. So far as possible all factors relative to previous illnesses, occupational or otherwise, poisoning, familial tendencies, age, sex, duration of symptoms and mode of onset have been considered with the findings on physical examination.

These cases have been considered as belonging to the group of malignant hypertension or diffuse arterial disease with hypertension, group 4. Each case had been carefully considered, and the data given in the abbreviated reports constitute only a bare abstract of the essential clinical features. The duration of symptoms was in no case greater than five years, and the known duration of the elevation of blood pressure was as short as nine months (case 20). Medication consisted, in most cases, only of sedatives such as chloral hydrate or barbiturates. When indicated, as when vomiting was persistent, intravenous medication had been given.

Laboratory data in respect to the range of elevation of the blood pressure, urinary excretion, presence of anemia and serologic examination are contained in table 1. In most instances the determinations were made while the patients were in the hospital and usually indicate findings made shortly before death. In case 26, the Kline and Kahn flocculation tests were used as serologic tests for syphilis. The Wassermann reaction was used in all other cases. Values for the blood urea were determined shortly before death. Often estimations had been made earlier, and similar values had not

5. (a) Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, *Am. Heart J.* **2**:597 (Aug.) 1927. (b) Keith, N. M.; Barker, N. W., and Kernohan, J. W.: Histologic Studies of the Arterioles in Various Types of Hypertension, *Tr. A. Am. Physicians* **46**:66, 1931. (c) Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, *Arch. Int. Med.* **41**:141 (Feb.) 1928. (d) Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**:395 (Sept.) 1929. (e) Wagener, H. P.: Sclerosis of the Retinal Arterioles, *Arch. Ophth.* **3**:335 (March) 1930; (f) Retinal Vascular Changes in Hypertension, *Ann. Int. Med.* **4**:222 (Sept.) 1930.

6. Major, R. H.: Renal Function in Arterial Hypertension, *Am. J. M. Sc.* **176**:637 (Nov.) 1928.

TABLE 1.—Laboratory Data for the Twenty-Six Cases Reported

Case	Blood Pressure, Mm. of Mercury				Specific Gravity of Urine		Albumin in Urine, Grade	Leukoocytes in Urine, Grade	Erythrocytes in Urine, Grade	Casts, Grade	Urea, Mg. in 100 Cc. Whole Blood	Creatinine, Mg. in 100 Cc. Whole Blood	Uric Acid, Mg. in 100 Cc. Whole Blood	Sulphates, Mg. in 100 Cc. Serum	Chlorides, Mg. in 100 Cc. Plasma	Urea Clearance*	Phenolsulphon-phthalein Excretion, per Cent	Hemoglobin, per Cent (Dare)	Hemoglobin, Gm. in 100 Cc. Blood	Erythrocytes, Millions per Cmm. of Blood	Leukoocytes per Cmm. of Blood	Flocculation Test for Syphilis (Blood)
	Maximal		Minimal		Lowest	Highest																
	Sys. toUe	Diast. toUe	Sys. toUe	Diast. toUe																		
1	255	165	200	150	1.006	1.025	1	1	34	1.9	78	..	51	16,000	Negative
2a†	240	160	210	160	..	1.018	..	1	34	1.8	70	..	4.71	10,400	Negative
2b†	34	7.4	4.6	70	..	4.00	16,500	Negative
3	240	140	222	130	63	2.6	4.5	5.52	12,600	Negative
4a	204	108	170	90	1.000	1.025	1	3	..	1	100	3.4	3.8	13.8	12,600	Negative
4b	238	154	220	144	1.020	..	2	1	..	1	115	4.1	4.6	11.2	12,600	Negative
5	240	120	1.001	..	2	1	101	4.5	3.75	16,800	Negative
6	220	162	216	120	1.011	..	4	1	148	6.6	3.30	12,400	Negative
7	220	162	168	128	1.015	..	4	1	384	16.0	4.07	8,800	Negative
8	230	140	1	1	242	10.4	2.56	8,200	Negative
9	230	165	150	110	1.013	..	1	1	224	9.5	3.48	8,700	Negative
10†	190	156	148	102	1.017	1.020	1	1	40	35.2	..	148.9	4.36	11,500	Positive
11	270	164	175	120	1.010	1.020	3	1	1	1	631	132	5.4	4.27	8,400	Negative
12	220	132	1.010	..	2	2	110	1.8	3.22	5,600	Negative
13	240	120	180	90	1.015	1.022	2	2	1	1	102	1.6	2.9	4.50	8,500	Negative
14	300	140	170	90	1.001	1.018	1	1	1	1	31	1.5	4.24	..	Negative
15a	158	110	118	80	1.007	..	1	1	271	17.0	4.45	..	Negative
15b	250	170	185	135	1.009	..	1	1	293	3.04	..	Negative
16	240	144	224	140	1.018	..	2	2	271	6.4	3.46	10,800	Negative
17	280	190	222	134	1.010	1.012	4	1	1	2	36	1.9	Negative
18	235	150	190	120	1.016	..	3	1	1	2	246	2.48	19,900	Negative
19	220	140	210	133	1.012	..	3	1	1	2	444	20.0	Negative
20a	112	80	Negative
20bs	180	110	1.016	1.030	0	1	1	2	40	2.0	2.48	19,900	Negative
21	260	150	220	124	1.013	..	2	1	1	1	132	2.4	Negative
22	230	165	225	160	1.013	..	2	1	1	1	243	9.2	Negative
23	250	110	190	110	1.010	..	2	1	3	..	20	13.2	..	6.0	3.03	19,800	Negative
24	200	130	170	120	1.002	1.030	2	1	1	..	215	1.5	5.20	11,200	Negative
25	200	150	3	1	1	1	150	3.0	4.20	7,000	Negative
26	192	126	172	110	1.005	..	3	1	1	1	222	13.6	..	10.5	3.76	13,000	Negative
27	280	175	200	95	1.010	..	4	1	1	..	303	20.3	..	20.3	4.69	18,400	Positive
27	280	175	200	95	1.013	..	3	1	256	20.3	3.33	9,800	Negative

* This indicates cubic centimeters of blood cleared of urea by the kidneys each minute.
† In each case in which a and b appear they indicate, respectively, first and second admission.
‡ The flocculation test for syphilis, on cerebrospinal fluid, was positive.
§ The urine contained arsenic and lead.
|| The urine contained arsenic.

been obtained. The figures for specific gravity of urine were obtained on numerous routine examinations or were obtained by estimation of the ability of the kidney to dilute or concentrate urine. In any case, these figures were obtained, unless otherwise stated, from examinations made shortly before death. The maximal and minimal blood pressures were either the extremes of blood pressure found on hourly examination for twenty-four hours or were simply the highest and lowest figures derived from a number of examinations.

Consideration of the abbreviated reports of cases and of the laboratory data given in table 1 suggests some features common to all of the cases. The ages of the patients ranged from 22 to 72; in sixteen of the twenty-seven cases death occurred when the patient was in the fourth or fifth decade of life. Three patients were younger than this at death; the others were older. Disability was of relatively short duration. The symptoms varied widely. In all of the cases, characteristic ocular findings as outlined by Wagener^{3f} were demonstrated. Except in cases 10, 17 and 22, there was evidence of impairment of excretion of nitrogenous products before death. In cases 10 and 22 there was no opportunity to obtain blood for examination in the late stages of the disease. Death in case 17 was probably the result of cerebral complications. The rapidity of onset of impairment of excretion of nitrogen in cases 19, 20 and 24 was striking; the patients had been under observation for considerable periods, and renal function was closely watched. In all cases, readings of blood pressure were invariably high, and there was little fluctuation in the level of either systolic or diastolic pressure.

Definite evidence of syphilitic infection was available in cases 10 and 26, and the history of miscarriages was suggestive in case 17. A history of either scarlatina or repeated attacks of tonsillitis was forthcoming in seventeen cases. One patient (case 15) had been treated five years previously for acute nephritis with edema. The presence of lead and arsenic in the urine in case 20 and of arsenic in case 26, and the administration of compounds of mercury in cases 24 and 15 were the only suggestions that metallic poisoning was a factor in the disease. Excessive use of tea, coffee, alcohol or tobacco was a significant feature only in cases 4, 8 and 20.

In all of the cases both kidneys or portions of them had been preserved in formaldehyde. From these, sections for microscopic examination were taken and stained with hematoxylin and eosin, Weigert's elastic tissue stain, van Gieson's stain, Mallory-Heidenhain's azan-carmin stain (as modified by Galantha) and sudan III with methylthionine chloride, U. S. P. (methylene blue). There was a noticeable increase in the thickness of the walls of the smaller arteries. To establish this with more certainty and to compare the increased thickness of the wall

with the diameter of the arterial lumen, various measurements were made with a Bausch and Lomb micrometer according to a method commonly used and described in detail by Kernohan.^{5a} In short, it consists in measuring the wall of the artery at four points, each situated at either end of lines drawn at right angles to each other through the center of the lumen. The average of these four measurements is then compared with the average diameter of the lumen. From these the ratio of the wall to the lumen is established. In each case at least ten arterioles, the outside diameters of which varied from 60 to 180 microns, were meas-

TABLE 2.—*Combined Weight of the Kidneys and the Ratio of the Walls to the Lumens of the Renal Arterioles*

Case	Malignant Hypertension		Controls	
	Weight, Gm.	Ratio of Wall to Lumen	Specimen	Ratio of Wall to Lumen
1.....	270	1:0.7	1	1:1.9
2.....	302	1:0.6	2	1:2
3.....	247	1:0.8	3	1:1.7
4.....	194	1:0.3	4	1:1.26
5.....	206	1:0.5	5	1:1.7
6.....	237	1:0.5	6	1:1.24
7.....	340	1:0.8	7	1:1.9
8.....	285	1:0.5	8	1:2.2
9.....	120	1:0.9	9	1:2.5
10.....	233	1:0.7		
11.....	243	1:0.4		
12.....	225	1:0.6		
13.....	221	1:0.5		
14.....	265	1:0.6		
15.....	Not available	1:0.6		
16.....	218	1:0.5		
17.....	268	1:0.7		
18.....	205	1:0.5		
19.....	380	1:0.3		
20.....	213	1:1.3		
21.....	388	1:0.5		
22.....	200	1:0.9		
23.....	309	1:0.6		
24.....	254	1:0.8		
25.....	341	1:0.6		
26.....	216	1:0.7		
27.....	289	1:0.7		

ured. Only those in which the planes of section passed at right angles through the vessel were measured. As controls, sections from the kidneys of nine young adults who had died as a result of accident or of cerebellar tumors were considered. In none of these was there evidence clinically or on postmortem examination of renal disease. Measurements of arterioles were made. These are included in table 2, with the similar ratio of wall to lumen found in the kidneys in the twenty-seven cases under consideration.

In twenty-six cases the weights of the kidneys were available; they are recorded in table 2. They varied considerably, but on the whole were surprisingly large. The average combined weight was 261 Gm. Although the body weights were available, their accuracy could be questioned, since some patients had been edematous when examined, whereas

others had vomited for varying periods before seeking medical attention. Concerning case 9 only the term contracted kidney might be used. In all other cases the kidneys could safely be considered to be of normal size.

There were some interesting findings on gross examination at necropsy. In all cases the heart had undergone hypertrophy. Evidence of healed tuberculosis of the lungs or lymph nodes was forthcoming in nineteen cases. Definite pyelonephritis was evident in cases 5, 25 and 27.

On microscopic examination more or less advanced disease was found in every case. It involved almost all of the structures of the kidney to a variable degree: glomeruli, tubules, arteries and interstitial tissue. The veins and venules did not seem involved, except for dilatation in some instances.

Changes in the glomeruli varied rather widely. In most cases either complete or partial hyalinization was present. In each case, one hundred or more glomeruli were examined, and the percentage of glomeruli presenting complete hyalinization varied, ranging from 2 to 35. Only in case 20 (symptoms of only nine months' duration) were no completely hyalinized glomeruli seen. In all of the cases many of the glomeruli showed partial hyaline change. The use of the term hyaline requires some explanation. Wells⁷ stated: "There is no one chemical compound hyaline which accumulating in cells or tissues produces a hyaline appearance. The limitations of the application of the term hyaline degeneration are not agreed on but, in general, it is used to apply to clear homogeneous pathological substances that possess a definite affinity for acid stains such as eosin." The preparations treated with van Gieson stain showed that even when the glomerulus had been completely replaced by this material, a connective tissue fiber could not be demonstrated throughout. In most cases a thick, reddish border could be seen, and, in a few, the reddish fibers extended into the center of the structureless nodules, from what was probably the point of entrance of the afferent artery. McGregor⁸ showed that connective tissue cells normally extend into the glomerulus in this region. Partial hyalinization of a glomerulus was frequently seen. Either one loop or the portion of the glomerulus that was continuous with the afferent artery had undergone this change.

Points of adhesion of glomerular loops to Bowman's capsule were frequently seen. In the preparation stained with azan-carmin it was noticed that at these points the blue-stained basement membrane of the

7. Wells, H. G.: *Chemical Pathology*, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

8. McGregor, Leone: *The Finer Histology of Normal Glomerulus*, *Am. J. Path.* 5:545 (Nov.) 1929; *Histological Changes in the Renal Glomerulus in Essential (Primary) Hypertension*, *ibid.* 6:347 (May) 1930.

capsule appeared continuous with the basement membrane of the glomerular loop, which in many instances appeared thickened. The van Gieson preparations failed to bring out a reddish fiber in these areas. With these adhesions, another feature could be noted: The glomerular loops were less numerous than in other glomeruli and appeared flatter. In most cases, however, glomerular capillary spaces were open and contained erythrocytes. Very few polymorphonuclear leukocytes were seen in these loops, and in no instance were erythrocytes or leukocytes seen in the capsular space. Neither was a definite formation of crescents seen, although in a few instances the point of

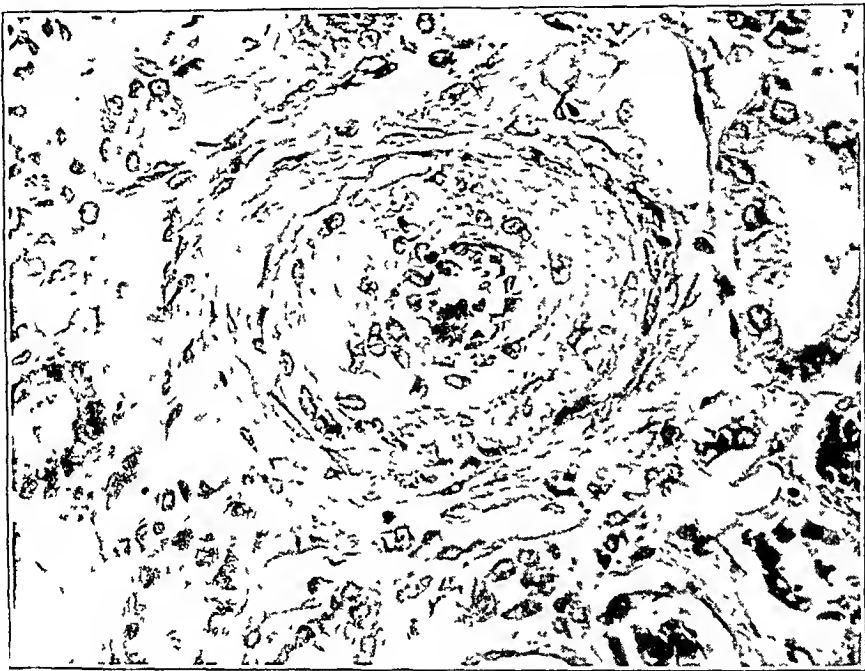


Fig 1 (case 11) —Changes in an artery of medium size; thickening of both medial and intimal tunics. Hematoxylin and eosin; $\times 300$.

adhesion of a glomerular loop to the capsule suggested this formation. Often there appeared to be many more nuclei of cells within the glomerulus than normally. This suggested that the entire glomerulus was larger than others. The apparent proliferation of endothelial and epithelial cells was not, however, a constant feature. Only rarely were lipid droplets identified in the glomeruli, even in those which exhibited the most extensive hyaline change.

The smaller arteries presented the most striking feature in all of the sections. Invariably the lumens were smaller than normal and, relative to the thickness of the wall, were very much diminished in size. Not a few were completely closed. The cause of this real or apparent thickening of the wall appeared to arise from a number of factors (fig. 1).

Beneath the endothelium there was usually a zone, in which few, and in many cases no, nuclei could be seen. This zone stained a uniform reddish pink in the hematoxylin-eosin, a light blue in the azan-carminé and a faint yellow in the van Gieson preparations. In this area of sections stained with sudan III, invariably there were a few fine, reddish points. Often a red band partly or completely encircled the vessel (fig. 2). The latter feature was rarely noticed in larger arteries. The internal elastic lamina could be seen clearly in the Weigert preparations. It was always thickened; in many instances it was broken and irregular (fig. 3) and in a few cases appeared to be separated into a number of

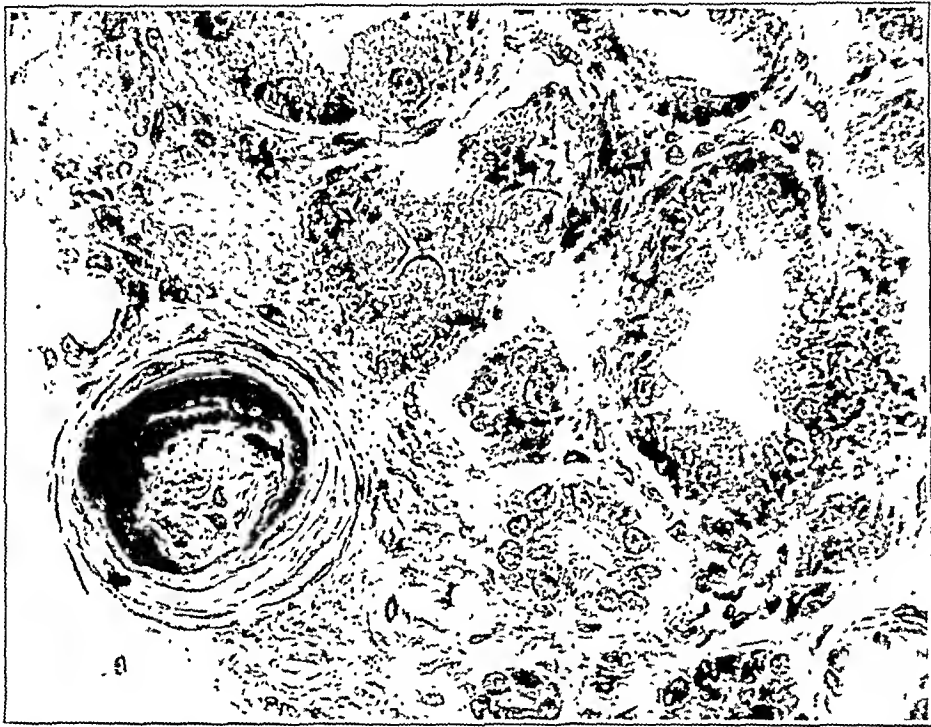


Fig. 2 (case 25).—Fatty change in the arterial wall. This appears as a dark smudge almost encircling the lumen. Sudan III; $\times 300$.

strands. The tunica media rarely presented degenerated areas. Only occasionally were reddish granules visible in the sudan III preparations. In most cases there was an apparent increase in the number of nuclei in the media. Only in the case of arteries of medium and large size was a definite, thickened fibrous band surrounding the adventitial tunica seen in the van Gieson preparations. Changes in the endothelium itself were somewhat difficult to determine. There was always the appearance of crowding of the nuclei of cells (fig. 4). It is evident that this might be due to proliferation of the endothelium, or it might be debated that originally these endothelial cells surrounded a larger lumen and were now forced into a smaller space by reason of the thickened walls.

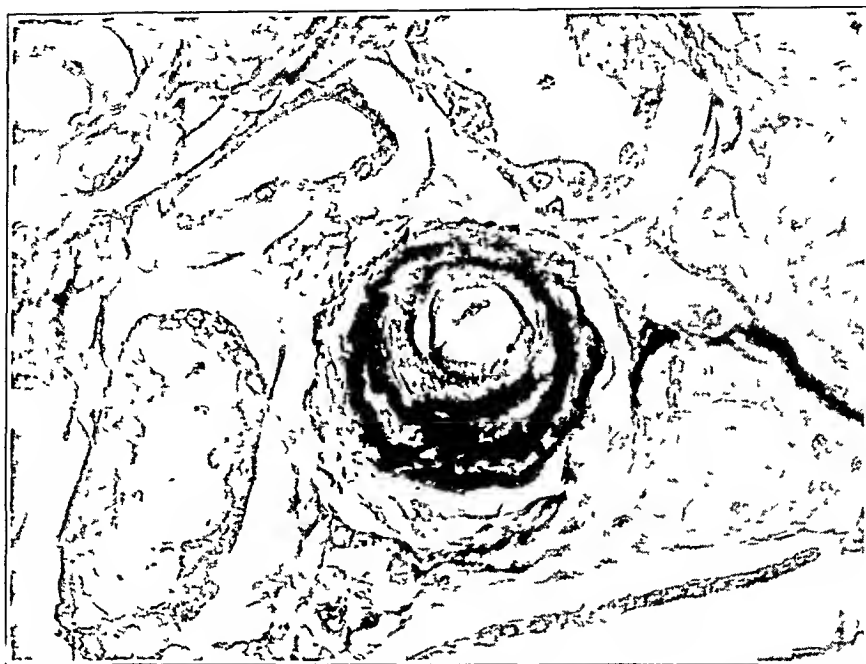


Fig 3 (case 13) —Thickening and fragmentation of the elastic lamina Weigert's elastic tissue stain, $\times 300$

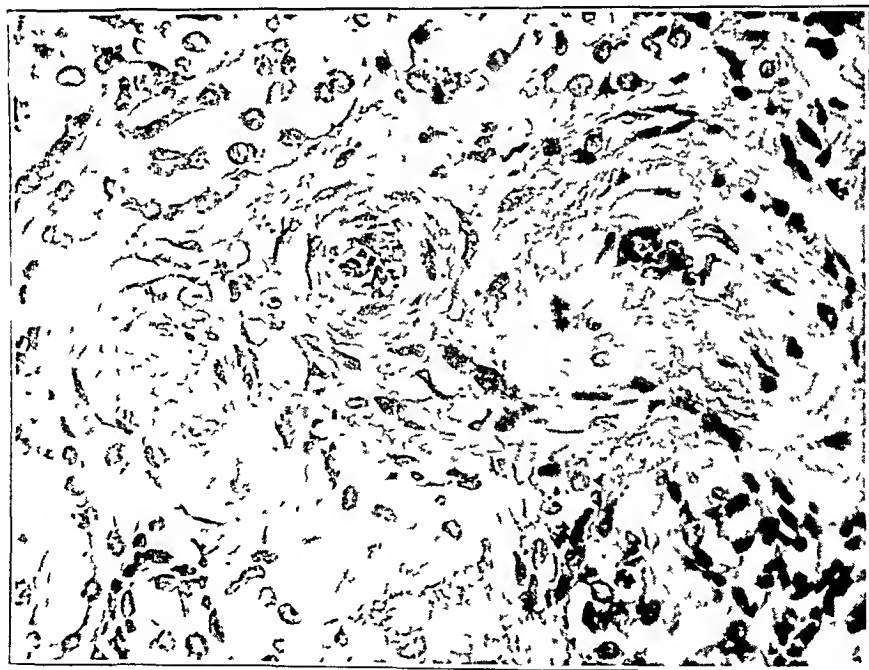


Fig 4 (case 18) —Thickening in the walls of the arterioles; there is an apparent increase in the number of the nuclei in the endothelium. Hematoxylin and eosin, $\times 300$

The ratios of the wall to the lumen are given in table 2. These are somewhat smaller than those obtained by Kernohan and by Pilcher and Schwab.⁹ Comparisons cannot be too literal. The material used by Kernohan^{5d} was obtained from muscle which had been taken for biopsy. Specimens here considered had been preserved for varying periods, and tissue fixatives may have had some effect. Furthermore, if the disease is rapidly progressive, it would be reasonable to postulate that the change in material obtained at necropsy would be more advanced than in that obtained for biopsy. It is probably safe to assert that the ratio of wall to lumen in these renal arterioles is reduced to less than

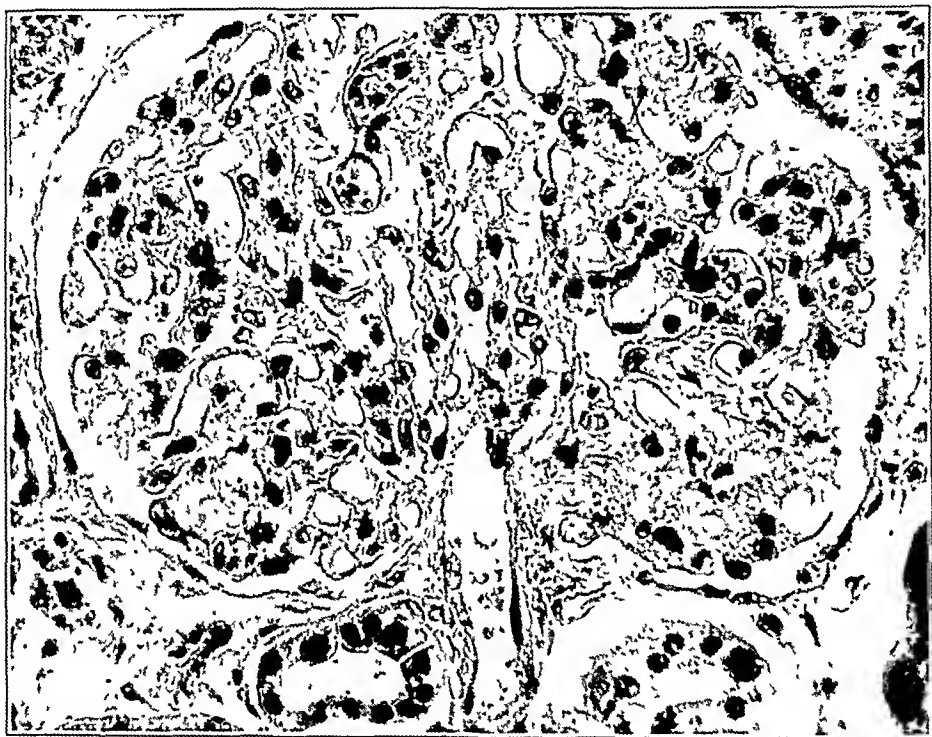


Fig. 5 (case 9).—Dilated vas afferens. Hematoxylin and eosin; $\times 300$.

1:1, and to appreciably less than that reported from examination of arterioles in voluntary muscle.

It has been mentioned that there was a dilated vessel continuous with the glomerular capillaries. In many cases this was the efferent vessel, but in a few instances examination of two or three successive sections established its identity as the afferent vessel (fig. 5). In such cases its wall presented a hyaline change similar to that seen in other small arteries in the section. Rarely was a small group of erythrocytes seen external to the endothelium, in the substance of the tunica media.

Tubular change, although less striking, was definite. In no case was swelling of the epithelial cells sufficient to occlude the lumen of the

9. Pilcher, J. F., and Schwab, E. H.: Arteriolar Changes in Essential Hypertension, *Texas State J. Med.* 28:665 (Feb.) 1933.

tubule. This had been suspected in cases in which concentrated solutions of dextrose had been given intravenously; Helmholtz¹⁰ found this experimentally in some animals to which concentrated solutions of sucrose had been given. In many areas the epithelium was flattened and the entire tubule dilated. Groups of dilated tubules of this sort were often seen and gave the appearance of small cysts. Masses were frequently seen within tubules. Usually they were homogeneous and structureless; they have been considered to be casts. Leukocytes, desquamated epithelial cells and erythrocytes often were found alone or surrounding the casts. Frequently, small granules could be identified in the cytoplasm of the epithelial cells, but rarely were lipoid droplets seen in the sudan III preparations. Sometimes in the azan-carmin preparations the basement membrane of the tubule appeared thickened.

Changes in the interstitial tissue could be found consistently. These varied in extent, but there was always more or less connective tissue between the tubules, especially in the medulla, with scattered groups of cells with small nuclei. These groups of small cells were mainly lymphocytes, with an occasional polymorphonuclear leukocyte and some plasma cells. They bore no clear relationship to glomeruli or tubules. In many cases the veins and capillaries around and between tubules were distended with erythrocytes.

In no case in which metallic poisoning or syphilis could have been considered as an etiologic factor was there a peculiar pathologic process. Tonsillitis or other infections had been noted in a high proportion of the cases. It is dangerous to interpret findings as being due to these infections. Evidences of tuberculosis were forthcoming in as high a proportion of cases, and it has not been suggested that this disease is an etiologic factor in the production of hypertension.

That changes in the blood or vascular structures of the body are factors in renal disease was suggested by Bright.¹¹ Gull and Sutton,¹² in reference to the constitutional form of Bright's disease, stated that the morbid condition begins as fibrosis in and around the small arteries and capillaries in the intertubular tissue. They also described a great change and degeneration of the arteries and the deposition of new material external to the lumen of the vessel. Johnson¹³ disagreed in part and considered that there is actual hypertrophy of the arterioles.

10. Helmholtz, H. F.: Personal communication to the author.

11. Bright: Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, *Guy's Hosp. Rep.* 1:338, 1836.

12. Gull, William, and Sutton, quoted by Gull, William: Arterio-Capillary Fibrosis, *Brit. M. J.* 2:673 (Dec. 21) 1872.

13. Johnson, George: The Muscular Arterioles: Their Structure and Function in Health and Certain Morbid States, *Brit. M. J.* 1:443 (April 14) 1877.

Ziegler¹⁴ stated that widespread sclerosis—sometimes necrosis in the intima of small arteries—produces contracted kidney. He mentioned changes in the tubules as a result. Ewald,¹⁵ in considering the changes in the smaller vessels in renal disease, measured the vessels, finding in normal vessels a ratio of wall to lumen of 0.1:1 or 0.2:1 and in renal disease a greatly changed ratio, sometimes 1.2:1. Thoma,¹⁶ in an investigation into the injury to the circulation of the blood in chronic interstitial nephritis, studied the new formation of connective tissue in the umbilical artery, the ductus Botalli and the arteries in the stumps of amputated limbs. He mentioned the appearance of a hyaline substance rich in cells under the intima. He found by perfusion that there was a decreased flow of fluid through the renal vascular bed. Mahomed¹⁷ mentioned a prealbuminuric stage of Bright's disease and considered poisoned blood as a factor in producing impeded circulation, which leads to high blood pressure. Allbutt¹⁸ found that in many of these cases of prealbuminuria Bright's disease developed.

Further consideration of the arterioles of the kidneys and of the systemic circulation has been reported by Kernohan, Anderson and Keith and by Murphy and his associates,¹⁹ who included measurements of the walls and lumens of smaller arteries and arterioles. They concluded that the ratio of the wall to the lumen was much decreased. Ghoreyeb²⁰ and Baehr, in investigating the condition of the arterial bed by perfusion and injection, found it contracted. The former found the same impediment to perfusion in spontaneous disease of the kidney

14. Ziegler, E.: Ueber die Ursachen der Nierenschrumpfung nebst Bemerkungen über die Unterscheidung verschiedener Formen der Nephritis und die darauf bezüglichen Theorien, *Deutsches Arch. f. klin. Med.* **25**:586, 1880.

15. Ewald, C. A.: Ueber die Veränderungen kleiner Gefässe bei Morbus Brightii, *Virchows Arch. f. path. Anat.* **71**:453 (Dec.) 1877.

16. Thoma, R.: Zur Kenntnis der Circulationsstörung in den Nieren bei chronischer interstitieller Nephritis, *Virchows Arch. f. path. Anat.* **71**:42 (Sept.) 1877; Ueber die Abhängigkeit der Bindegewebsneubildung in der Arterienintima von den mechanischen Bedingungen des Blutumlaufes, *ibid.* **95**:294 (May) 1880; **104**:209, 1886.

17. Mahomed, F. A.: Some of the Clinical Aspects of Chronic Bright's Disease, *Guy's Hosp. Rep.* **24**:363, 1879.

18. Allbutt, Clifford: *Diseases of the Arteries, Including Angina Pectoris*, London, The Macmillan Company, 1915.

19. Murphy, F. D., and Grill, John: So-Called Malignant Hypertension, a Clinical and Morphologic Study, *Arch. Int. Med.* **46**:75 (July) 1930. Murphy, F. D.; Grill, John; Pessin, Benjamin, and Moxon, G. F.: Essential (Primary) Hypertension, *Ann. Int. Med.* **6**:31 (July) 1932.

20. Ghoreyeb, A. A.: Studies on the Circulation: I. The Effect of Disease on the Renal Arterial Bed, *J. M. Research* **35**:87 (Sept.) 1916; A Study of the Mechanical Obstruction to the Circulation of the Kidney Produced by Experimental Acute Toxic Nephropathy, *J. Exper. Med.* **18**:29 (July) 1913.

produced by potassium chromate. In 1904, Jores²¹ emphasized the degenerative nature of the arterial changes in contracted kidney. From Fahr,²² however, came the greatest emphasis on the distinction between benign and malignant nephrosclerosis. The latter occurred in younger persons. Microscopically, there was an endarteritic and necrotizing process in the arterioles. These vessels were often narrowed and many times completely closed. Arteriosclerosis of the larger arteries was also present.

It is to be remembered, as Johnson suggested, that occlusion of the lumens of arteries may not be so great as it seems to be in some sections. Shapiro²³ found, by perfusion, that india ink passed through arteries which were apparently occluded. He further stated that although ischemia undoubtedly is present in nephrosclerosis, it is not the basis of the characteristic pathologic change. He considered direct hyperemia to be the cause and distinguished the appearance of well filled veins and capillaries from the condition seen in chronic passive congestion of the kidney. Ettinger²⁴ produced contraction of arterioles, fibrosis and hyalinization of some glomeruli, with occasional areas of fatty degeneration and adhesions of glomerular loops to Bowman's capsule. Bell and Clawson²⁵ stated that in the glomeruli of four of a group of thirty-six cases which constituted their renal group showing hypertension, there were acute inflammatory changes such as are found in glomerulonephritis. They commented on the evidence of most rapid closure of small arteries and arterioles.

In an examination of fifteen cases of essential hypertension, Pilcher and Schwab found a difference between the arteriolar change seen in the kidney and spleen and that seen in the liver and pancreas. In the former two organs, degenerative changes were prominent. In an interesting report of a case in which a kidney was removed because of hematuria and in which death occurred shortly afterward, but in which clinical studies following the emergency nephrectomy established the

21. Jores, L.: Ueber Arterienveränderungen bei Nephritikern, *Verhandl. d. deutsch. path. Gesellsch.* **7**:174, 1904; Ueber den pathologischen Umbau von Organen (Metallaxie) und seine Bedeutung für die Auffassung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrozirrhosen) und der Arteriosklerose, *Virchows Arch. f. path. Anat.* **221**:14, 1916.

22. Fahr, T.: Zur Pathogenese der akuten Glomerulonephritis, *Deutsche med. Wchnschr.* **52**:735 (April) 1926.

23. Shapiro, P. F.: Malignant Nephrosclerosis, *Arch. Int. Med.* **48**:199 (Aug.) 1931.

24. Ettinger, G. H.: The Action of Janus Green upon Blood Vessels, *Quart. J. Exper. Physiol.* **22**:167 (Aug.) 1932.

25. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, *Arch. Path.* **5**:939 (June) 1928.

diagnosis of malignant arterial hypertension, Weiss, Parker and Robb²⁶ stated that there was proliferation of the glomeruli of definite degree and a more marked degree of cellular infiltration in the kidney that was removed first.

The medical literature of the last two decades contains many articles on the various features presented by kidneys removed in cases of hypertension. Since the etiology of the primary condition remains obscure, the causal factors are also conjectural. Volhard²⁷ mentioned the possibility that an inflammatory factor aggravated or was added to pre-existing vascular disease. In considering the pathogenesis of acute glomerulonephritis, Fahr showed that early in this condition (three days after its onset) there were evident changes in the afferent and efferent glomerular arteries. Gaskell²⁸ had shown much earlier that in many cases of acute glomerular nephritis fatty and hyaline changes could be found in the intima of the afferent artery of the glomerulus. Löhlein²⁹ emphasized changes in this artery and described dilatation of its lumen. Klemperer and Otani³⁰ agreed with Löhlein that the tempo of the process distinguishes mild arterial disease from malignant nephrosclerosis. They considered a group in which they postulated an inflammatory factor. Herxheimer³¹ and Stern³² reported cases of arteriolonecrosis in which they considered that there had been no arteriolitis, and that the rapid development of renal insufficiency was the result of a purely necrotizing process. Baehr and Ritter³³ considered that there can develop in chronic nephritis vascular alterations as severe as those in primary disease of the intrarenal vessels. Fishberg³⁴ asserted that many types of arteriosclerosis and hypertrophy of the muscular layer can

26. Weiss, Soma; Parker, Frederic, Jr., and Robb, G. P.: A Correlation of the Hemodynamics, Function and Histologic Structure of the Kidney in Malignant Arterial Hypertension with Malignant Nephrosclerosis, *Ann. Int. Med.* **6**:1599 (June) 1933.

27. Volhard, F.: *Die doppelseitigen hematogenen Nieren-Erkrankungen*, Berlin, Julius Springer, 1918, vol. 8.

28. Gaskell, J. F.: On the Changes in Glomeruli and Arteries in Inflammatory and Arterio-Sclerotic Kidney Disease, *J. Path. & Bact.* **16**:287, 1912.

29. Löhlein, M.: Zur vasculären Nierensklerose, *Med. Klin.* **2**:1042, 1916.

30. Klemperer, Paul, and Otani, Sadao: Malignant Nephrosclerosis (Fahr), *Arch. Path.* **11**:60 (Jan.) 1931.

31. Herxheimer, Gotthold: Ueber Arteriolonekrose der Nieren, *Virchows Arch. f. path. Anat.* **251**:709, 1924.

32. Stern, Max: Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der grossen bunten Niere, *Virchows Arch. f. path. Anat.* **251**:718, 1924.

33. Baehr, George, and Ritter, S. A.: Arterial Supply of the Kidney in Nephritis, *Arch. Path.* **7**:458 (March) 1929.

34. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, *Arch. Int. Med.* **40**:80 (July) 1927.

develop in glomerulonephritis. Russel³⁵ considered that degenerative vascular changes supervene on hypertrophy.

Changes in the tubules are usually found, and these have also been related to the alteration in circulation, since any impairment of the blood supply of the glomerulus must affect the tubule proceeding from it. Jores disagreed with the usual interpretation and asserted that the atrophy which resulted was atrophy from inactivity. He also considered elastic hyperplasia and fatty degeneration of the arteriolar walls as factors in the production of the disease. In the main, Aschoff³⁶ agreed with this interpretation.

In three of the cases on which this study is based evidence of pyelonephritis was present. Braasch³⁷ reported four cases of urinary obstruction from various causes in which at necropsy thickening of the tunica intima of the arteries could be demonstrated. Russel, in an exhaustive investigation of a large group of cases, stated: "The type of nephritis which is closely associated with chronic degeneration of arteries is, therefore, also found in association with compression of the renal cortex by hydronephrosis, tumors or cysts."

REPORT OF CASES

CASE 1.—A white housewife, aged 45, first noted weakness of the right side of the body. Other symptoms were impaired vision, dyspnea, edema and headache. The significant findings on physical examination were an enlarged heart, an enlarged liver, right hemiparesis and edema. Later, paresis increased. Previous illnesses included scarlatina and influenza. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, irregularity of the caliber of the retinal arteries, exudates and hemorrhages were present. A grandparent had died of a stroke.

CASE 2.—A white housewife, aged 54, first noted general weakness. Other symptoms were impaired vision and a burning feeling in the feet and edema. Significant findings on physical examination were infected teeth, an enlarged heart and edema of the feet. Later paresthesia of the right side of the body developed. Previous illnesses included pertussis, scarlatina and a condition which probably was rheumatic fever. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The patient's father had died of a stroke.

CASE 3.—A white housewife, aged 42, first noted anasarca. Other symptoms were headache, orthopnea and nocturia. Significant findings on physical examination were an enlarged heart, pericardial friction rub, ascites and edema. Later

35. Russel, Dorothy: A Classification of Bright's Disease, Medical Research Council, Special Report, Series no. 142, London, His Majesty's Stationery Office, 1929.

36. Aschoff, Ludwig: The Pathogenesis of the Contracted Kidney, *Arch. Int. Med.* **12**:723 (Dec.) 1913.

37. Braasch, W.: Ueber die klinischen Erscheinungen bei langendauernder Anurie, *Deutsches Arch. f. klin. Med.* **103**:488 (Aug.) 1911.

progressive dyspnea appeared. Previous illnesses included typhoid fever, tonsillitis and influenza. Sclerosis of the peripheral arteries was graded 1. Severe neuroretinitis, secondary optic atrophy, retinal arteriosclerosis, thrombosis of the retinal veins, exudates and hemorrhages were present. No history of a familial tendency to disease was obtained.

CASE 4.—A white farmer, aged 46, first noted edema. Other symptoms were orthopnea, nocturia and dyspnea. Significant findings on physical examination were emaciation, infected tonsils, ascites and râles in the lower part of the thorax. Later dyspnea progressed and breathing became irregular. Previous illnesses included influenza, jaundice and cholecystitis. Sclerosis of the peripheral arteries was graded 2. Moderate neuroretinitis and moderate sclerosis of the retinal arteries were present. Each of the patient's parents had died of a stroke. The effect of mercury possibly entered into this case. The patient used mild mercurous chloride for a cathartic. He also drank tea and coffee in large amounts.

CASE 5.—A white grain-buyer, aged 62, first noted occipital pain. Other symptoms were loss of memory, dyspnea, general weakness, edema and failing vision. Significant findings on physical examination were restlessness and presystolic and postsystolic cardiac murmur. Later the condition progressed rapidly. There was no history of previous illnesses. Sclerosis of the peripheral arteries was graded 4. Neuroretinitis, a few retinal hemorrhages and cotton-wool and star-shaped exudates were present. The patient's father had died of tuberculosis, and his mother of arteriosclerosis.

CASE 6.—A Negress, a housewife, aged 44, first noted asthmatic attacks. Other symptoms were dyspnea and a productive cough. Significant findings on physical examination were infected tonsils and râles in the lower part of the thorax. Orthopnea developed later. Previous illnesses included pneumonia, gonorrhea and tonsillitis. Sclerosis of the peripheral arteries was graded 1. Neuroretinitis was present.

CASE 7.—A white laborer, aged 40, first noted spells of choking. Other symptoms were pain in the right lower part of the back. Significant findings on physical examination were an enlarged heart and gallop rhythm. Later progressive dyspnea developed. The patient had previously had diphtheria. Sclerosis of the peripheral arteries was graded 3. Neuroretinitis, sclerosis of the retinal arteries and exudates were present. The patient used coffee and tobacco.

CASE 8.—A white railway conductor, aged 44, first noted pain in the upper part of the abdomen. Other symptoms were dyspnea, orthopnea, nocturia, headache and nausea. Significant findings on physical examination were pallor, dyspnea, râles over the lower part of the thorax and an enlarged, tender liver. Later the condition became rapidly worse. Previously, the patient had had renal colic. Sclerosis of the peripheral arteries was graded 1. There were edema of the disks (1 diopter) and sclerosis of the retinal arteries, grade 3, with distinct retinitis. The patient's mother had died of a stroke, and his brother had heart trouble. The patient used tea and coffee to excess.

CASE 9.—A white farmer, aged 39, first noted headache. Other symptoms were nocturia, impaired vision, loss of weight and orthopnea. The significant findings on physical examination were an enlarged heart and an enlarged liver. Later the condition became rapidly worse. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 1. Hyperemia and edema of the optic disks and sclerosis of the retinal arteries were present. The patient's

father had died of a stroke, and the patient's wife had died of tuberculosis. The patient used alcohol, tea and tobacco in moderation.

CASE 10.—A white truck driver, aged 23, first noted paralysis of the right side of the body. Other symptoms were headache and weakness. The significant finding on physical examination was weakness of the right side. The patient died suddenly, one year after the examination. Previous illnesses included appendicitis and syphilis. Sclerosis of the peripheral arteries was graded 1. Marked edema of the optic disks and constriction of the retinal arteries were present. No history was obtained of a familial tendency to disease. The patient had been given arsenic.

CASE 11.—A white farmer, aged 48, first noted headache. Other symptoms were nocturia and orthopnea. On physical examination, the only significant finding was pericardial friction rub. Later, steadily and rapidly, the condition became worse. Previous illnesses included pneumonia and rheumatism. Sclerosis of the peripheral arteries was graded 4. Edema of the optic disks and sclerosis of the retinal arteries were present.

CASE 12.—A white man, a government official, aged 50, first noted general fatigue. Other symptoms were dyspnea and headache. On physical examination the only significant finding was precordial murmur. Later the headache became increasingly severe. Sclerosis of the peripheral arteries was graded 2. Hyperemia and edema of the optic disks and sclerosis of the retinal arteries were present. The patient's father and two brothers had died of a stroke.

CASE 13.—A white farmer, aged 72, first noted blindness of the right eye. Other symptoms were dizziness, dyspnea and polyuria. On physical examination, significant findings were infected teeth and enlargement of the prostate gland. The condition rapidly became worse. Previous illnesses included influenza and intestinal hemorrhages. Sclerosis of the peripheral arteries was graded from 1 to 2. Sclerosis of the retinal arteries, graded from 2 to 3, edema of the optic disks, hemorrhages and exudates were present. The patient's father had died of a disease of the bladder; one brother had died of stroke and another of tuberculosis.

CASE 14.—A white housewife, aged 57, had a nervous breakdown as the first evidence of disease. Other symptoms were palpitation, dyspnea, nocturia, precordial pain and headache. The significant findings on physical examination were enlargement of the heart and thyroid gland and systolic murmur. The condition rapidly became worse. Previous illnesses included influenza and tonsillitis. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The patient's father had died of paralysis.

CASE 15.—A white man, a factory worker, aged 24, first noted impairment of vision. Other symptoms were headache, nocturia, edema, epistaxis and vomiting. Significant findings on physical examination were irregular breathing and systolic cardiac murmur. Later the dyspnea increased. Previous illnesses included appendicitis, tonsillitis and acute nephritis with edema. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, constriction of the retinal arteries and retinitis were present.

CASE 16.—A white man, a clothing worker, first noted generalized weakness. Other symptoms were blurring of vision, dyspnea, nocturia and nausea. Physical examination disclosed nothing of note. Right hemiplegia developed later. Previous illnesses included scarlatina, pleurisy, malaria, typhoid fever, influenza and tonsil-

litis. Sclerosis of the peripheral arteries was graded 1. Hyperemia and edema of the optic disks and retinitis were present. The patient's grandmother had died of apoplexy.

CASE 17.—A white housewife, aged 22, first noted gastric trouble. Other symptoms were backache, loss of weight and nocturia. Significant findings on physical examination were purpuric areas. A week later the patient became unconscious; she died in coma four days afterward. Previous illnesses included measles and typhoid fever. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, constriction of the retinal arteries and hemorrhages and exudates were present. The patient's grandmother had died of diabetes. The patient had had three miscarriages.

CASE 18.—A white man, aged 44, first noted headache and vomiting. On physical examination the only significant finding was pulmonary edema. Severe neuroretinitis and sclerosis of the retinal arteries were present. The patient died within two days after his admission to the hospital.

CASE 19.—A white farmer, aged 39, first noted headache. Other symptoms were loss of vision, dyspnea and vomiting. On physical examination, significant findings were infected teeth, râles in the lower part of the thorax and enlargement of the liver. Later the dyspnea increased. The patient had previously had scarlatina. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries and retinitis were present. One living brother of the patient had hypertension.

CASE 20.—A white farmer, aged 39, first noted pains in the neck. Other symptoms were irregular fever, pains in the legs, weakness and numbness of the left hand, nocturia and edema. Significant findings on physical examination were epigastric tenderness, atrophy of the muscles, loss of tendon reflexes and enlargement of the liver. Later, mastitis, increase in fever and progressive weakness developed. Previous illnesses included tonsillitis and gonorrhea. Sclerosis of the peripheral arteries was graded from 0 to 1. The optic disks were hyperemic and exudates were present. The possible effect of lead and of arsenic had to be considered in this case. The patient used tobacco and alcohol and drank large amounts of tea and coffee.

CASE 21.—A white man, a postal clerk, aged 39, first noted headache. Other symptoms were insomnia, retrosternal pain, dyspnea, mental confusion and dimness of vision. Significant findings on physical examination were râles over the bases of the lungs and systolic cardiac murmurs. The patient previously had had tonsillitis. His death occurred a few days after registration. Neuroretinitis and sclerosis of the retinal arteries were present. The patient's father had died of tuberculosis and one living brother had heart disease.

CASE 22.—A white plumber, aged 29, first noted cramping pain in the left portion of the abdomen. Other symptoms were anginal pain, visual scotoma, blurring of vision and headache. Significant findings on physical examination were infected teeth and gallop rhythm. The condition became rapidly worse. The patient previously had had tonsillitis. Constriction of the retinal arteries, hyperemia and edema of the optic disks, exudates and hemorrhages were present. The patient's mother, who was living, had high blood pressure; his father had died of a stroke. The possible effect of lead had to be considered in this case.

CASE 23.—A white farmer, aged 56, first noted headache. Other symptoms were nocturia, nausea and vomiting. Significant findings on physical examination

were infected teeth and tonsils and enlargement of the heart, liver and prostate gland. Later, urinary retention developed, and the condition became rapidly worse. Previously the patient had had influenza. Sclerosis of the peripheral arteries was graded 1. Edema of the optic disks, retinitis and sclerosis of the retinal arteries were present. One brother had had tuberculosis; two living sisters had hypertension. Suprapubic cystostomy was performed.

CASE 24.—A white man, a real estate dealer, aged 41, first noted mild fatigue. Other symptoms were cough, nausea, vomiting, edema and dyspnea. Significant findings on physical examination were infected tonsils and enlargement of the heart and liver. Later, vomiting progressively increased in severity, and coma appeared. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, retinitis and thrombosis of the retinal veins were present. One living brother had tuberculosis.

CASE 25.—A white, road-building contractor, aged 37, first noted transient hematuria. Other symptoms were headache, colicky abdominal pain, failing vision, nocturia and cough. Significant findings on physical examination were infected teeth and enlargement of the heart. Later, edema, pericarditis and pneumonia developed. Previously the patient had had gonorrhea. Sclerosis of the peripheral arteries was graded 2. Edema of the optic disks, sclerosis of the retinal arteries and retinitis were present. The patient's mother, who was living, had heart trouble. The man used tobacco to excess.

CASE 26.—A white automobile dealer first noted slight weakness. Other symptoms were impaired vision, nocturia and mental confusion. Significant findings on physical examination were dry, red skin, otitis media, infected tonsils, an enlarged heart, edema and twitching of the muscles. Later, progressive dyspnea and edema developed. Previously the patient had had tonsillitis. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, sclerosis of the retinal arteries, hemorrhages and exudates were present. The possible effect of arsenic must be considered in this case. The patient's wife had had two miscarriages.

CASE 27.—A white housewife, aged 51, first noted precordial pain. Other symptoms were headache, fatigue, vomiting and impaired vision. Significant findings on physical examination were enlargement of the heart, pericardial friction rub and consolidation of the bases of the lungs. Later, progressive dyspnea developed. Previously, the patient had had influenza. Sclerosis of the peripheral arteries was graded 3. Edema of the optic disks, constricted retinal arteries and retinitis were present.

SUMMARY

In a group of cases of malignant hypertension the findings on examination of microscopic sections consisted in diffuse changes involving glomeruli, tubules, arterioles, arteries and interstitial tissue. The most prominent changes occurred in the arterioles; they consisted in extreme narrowing of the lumen, apparent increase in the numbers of endothelial cells, subendothelial fatty and hyaline degeneration, apparent thickening of the tunica media and an increased amount of connective tissue, chiefly in the tunica adventitia. The ratios of the wall to the lumen of the renal arterioles were markedly reduced. The kidneys were not markedly or uniformly decreased in size.

CHANGES OF THE DIGESTIVE TRACT IN UREMIA

A PATHOLOGIC ANATOMIC STUDY

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Although the gastro-intestinal manifestations of uremia have attracted much attention and numerous contributions deal with their symptomatology; the literature contains but few systematic studies of the underlying pathologic-anatomic changes. The severe necrotizing and ulcerative lesions of the intestine especially are of great interest and have caused much controversy as to their frequency and pathogenesis. While some authors consider a dysentery-like inflammation of the colon and, partially, also of the ileum as one of the most characteristic post-mortem observations in uremia, Siegmund,¹ in a recent review on the subject, came to the conclusion that the severe changes are rare. This is in agreement with statements found in the older literature (Pineau,² Fédou,³ Fischer⁴ and others). Working in Kundrat's institute, Fischer found ulceration of the colon in only 4 of 17 cases of uremia. The majority of the patients showed only a swelling of the mucosa with superficial, microscopic areas of necrosis. The blood vessels of the sub-mucosa were dilated, and the mucosa contained hemorrhages. The hemorrhagic character of the uremic lesions of the intestine has also been stressed by French investigators (Mathieu and Roux⁵ and others). Siegmund described as the most common intestinal observation in uremia a diffuse edema of the mucosa with pseudomelanotic pigmenta-

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1. Siegmund, H., *Einfache Entzündungen des Darmrohres*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie*, Berlin, Julius Springer, 1929, vol. 4, pt. 3, p. 261.

2. Pineau, M.: *Des hémorragies gastro-intestinales d'origine urémique*, Thèse de Paris, 1899.

3. Fédou, A.: *Contribution à l'étude des hémorragies intestinales au cours de l'urémie*, Thèse de Toulouse, 1899.

4. Fischer, J.: *Zur Kenntnis der Darmaffektionen bei Nephritis und Uraemie*, Virchows Arch. f. path. Anat. **134**:380, 1893.

5. Mathieu, A., and Roux, J.: *Sur un cas d'ulcérations urémiques de l'estomac et de l'intestin grêle*, Arch. gén. de méd. **7**:14, 1902.

tion. The majority of the reports on uremic necrosis and ulceration of the intestine are based on the study of a single case or of a few cases only (Chiari,⁶ Siegmund, Würth⁷ and others). Pilliet,⁸ Lancereaux,⁸ Mathieu and Roux⁵ and Lubarsch⁹ referred to uremic changes in the stomach.

The attempts to explain the uremic lesions of the gastro-intestinal tract center about the compensatory elimination through the stomach and intestine of metabolic waste products which the kidneys have failed to excrete. In 1859, Treitz¹⁰ formulated a theory which, though refuted by some authors, has held sway up to the present time. According to him the urea which is excreted through the glands of the intestinal mucosa in uremia is broken up in the lumen of the intestine into ammonia and carbonic acid. Ammonium carbonate, which exerts a caustic action on the mucosa, is formed. The experimental production of severe lesions of the intestine by the oral administration of ammonia water seemed to support Treitz's explanation. Hlava¹¹ was the first to attack the theory of Treitz, stressing the importance of a primary thrombosis of the small vessels of the intestinal mucosa. Fischer was not able to confirm Hlava's interpretation and considered the thrombi secondary to the necrosis and ulceration. Fischer assumed that the disturbed renal function led to an enterocolitis which, in some instances, became so severe as to cause necrosis and ulceration. He did not, however, explain the relations between the enterocolitis and the renal insufficiency. Mathieu and Roux considered the possibility of bacterial toxins as a potent factor in causing the severe intestinal changes. They pointed to the enormous dilatation of the venules and capillaries in the region of the ulcerations and suggested that this dilatation might diminish the vitality of the tissue. According to Pineau several factors act together to bring about the uremic necrosis and ulceration. These factors are: alteration of the blood vessels and perivascular tissue, irritation of the nerves and increase of the blood pressure. The significance

6. Chiari, H.: Ein Beitrag zur Lehre von der Uraemie, *Verhandl. d. deutsch. path. Gesellsch.* **15**:207, 1912.

7. Würth, W.: Ueber die Bedeutung der Arteriolenklerose für die Entstehung uraemischer Nekrosen, *Virchows Arch. f. path. Anat.* **284**:175, 1932.

8. Quoted by Konjetzny, G. E., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie*, Berlin, Julius Springer, 1928, vol. 4, pt. 2, p. 934.

9. Lubarsch, O.: *Pathologische Anatomie und Histologie der entzündlichen Erkrankungen des Magens*, *Verhandl. 6. Tagung der Gesellschaft f. Stoffwechsel u. Verdauungskrankheiten*, Berlin, 1926.

10. Treitz: Ueber uraemische Darmaffektionen, *Vrtljschr. f. prakt. Heilk.* **64**: 143, 1859.

11. Hlava, quoted by Fischer.⁴

of the high blood pressure has also been emphasized by Lemierre¹² and by Bensaude, Cain and Antoine.¹³ In 1923 Leyrat¹⁴ again referred to the urea as causing the uremic ulcerations of the intestine. Having produced a uremic-like condition in dogs by the slow intravenous injection of large amounts of urea, Streicher¹⁵ observed what he called a marked enteritis and congestion of the intestinal mucosa. From his illustration one obtains the impression that the mucosa was hemorrhagic rather than congested. Microscopic observations of the intestine are not given by Streicher.

In 1 case of chronic glomerulonephritis and in 3 cases of malignant nephrosclerosis with necrotizing lesions in the intestine Siegmund found arteriolonecrosis in the submucosa; this he considered as essential in causing the necrosis of the mucosa by interfering with the blood supply. Würth observed similar severe arteriolar changes in 1 case of arteriosclerotic contracted kidney with focal areas of necrosis and ulceration in the large intestine. In 2 other cases of uremia, 1 of which showed extensive necrosis of the mucosa of the esophagus, stomach, pharynx and small and large intestine Würth, however, failed to find the arteriolar necrosis of the submucosa and preferred, therefore, the old theory of a toxic cause to Siegmund's theory of vascular origin.

Volhard,¹⁶ who distinguished between acute eclamptic pseudo-uremia, chronic pseudo-uremia and true chronic uremia, classified the lesions of the digestive tract with the manifestations of the true uremia. The true uremia results from the renal insufficiency and auto-intoxication, while the two forms of pseudo-uremia are vascular and not directly related to the breaking down of the function of the kidneys. Volhard stated that in true chronic uremia there is a great tendency to infectious processes as terminal complications, admitting that the toxic action of retained endogenous waste products cannot be completely disposed of in explaining the intestinal changes.

From the review of the literature it is apparent that many additional experimental, biochemical and morphologic studies are required before the question of the uremic lesions of the digestive tract can be considered settled. The chemical aspects of uremia have recently been

12. Lemierre, A., and Piédelièvre, E.: Les ulcérations gastro-intestinales urémiques, leur rapport avec l'azotémie, *Gaz. d. hôp.* **94**:1437, 1921.

13. Bensaude, R.; Cain, A., and Antoine, E.: Contribution à l'étude de la recto-colite hemorrhagique d'origine urémique, *Ann. de méd.* **7**:41, 1920.

14. Leyrat, L.: Pathogénie des ulcérations gastro-intestinales urémiques, Thèse de Paris, 1923.

15. Streicher, M.: Experimental Uremia-Uremic Enteritis, *Arch. Int. Med.* **42**:835 (Dec.) 1928.

16. Volhard, F.: Die Uraemie, in von Bergmann, G., and Staehlin, R.: *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 1.

reviewed by Volhard, to whom we owe much for the better understanding of the complex problem of uremia, and who has carried a great step forward the conception inaugurated by the work of Ascoli and Widal. This article is devoted to the morphology of the uremic lesions of the digestive tract.

MATERIAL

The study is based on 136 consecutive cases of uremia which came to autopsy between Jan. 1, 1929, and April 1, 1933. According to the underlying renal lesion the cases are distributed as follows: acute glomerulonephritis, 13; subacute glomerulonephritis, 13; chronic glomerulonephritis, 31; malignant nephrosclerosis, 72; pyelonephritis, 5; polycystic kidneys, 2. The high incidence of malignant nephrosclerosis is due to the high percentage of Negroes. As pointed out by one of us (Dr. Jaffé¹⁷), malignant nephrosclerosis is common in the colored race.

MACROSCOPIC OBSERVATIONS

The macroscopic changes which the digestive tract presented in the 136 cases of uremia varied considerably in extent and intensity, and, in general, there seemed to be no parallelism between the severity of these changes and the duration of the uremic state. In describing the changes we shall start with the mild forms and then gradually proceed to the severe ones.

In 37 cases (27.1 per cent) the essential change consisted of a slight to moderate edema of the submucosa which chiefly affected the large intestine. The mucosa of the ileocecal valve and of the cecum was often injected, and the inner surface was covered with an increased amount of mucus. In the stomach the excess of mucus was sometimes marked. In a few instances the mucosa of the ileum was raised to circular folds, the crests of which were deeply injected. The content of the large intestine was usually formed.

In 72 cases (52.9 per cent) hemorrhages were found in the mucosa of the digestive tract. Figure 1 *A* illustrates the distribution of these hemorrhages. Though no part between the lower half of the esophagus and the anus was spared, the stomach, ileum, cecum and colon were most frequently affected. Thirty-eight cases showed only single, loosely scattered petechiae from the size of a pinhead to about 4 or 5 mm. in diameter. In 22 cases the hemorrhages were more marked, while in 11 they were extensive. In the latter cases the picture was very characteristic. The deep red mucosa was raised to thick folds which were formed by the edematous submucosa, and the hemorrhagic areas shining through the serosa could be seen from the outside of the intestine. The

17. Jaffé, R. H.: Hypertonie und maligne Nephrosclerose bei Negeren, *Centralbl. f. allg. Path.* 55:209, 1932.

intestinal content was bloody, dark reddish-brown or tarry and semi-liquid. In the milder cases the mucus which covered the inner surface of the mucosa was often stained with blood.

Whether single or diffuse, the hemorrhages undoubtedly preceded the pseudomembranous and ulcerative lesions to be discussed next. In many instances one could see in the center of a hemorrhagic area a fine veil-like and light grayish-brown membrane which could easily be wiped off, leaving a slightly roughened, shallow depression. These fine membranes appeared first in the region of the ileocecal valve and at the height of the folds.

In 27 cases (19.8 per cent) pseudomembranous and ulcerative changes were present. Their distribution is shown in figure 1 *B*. In

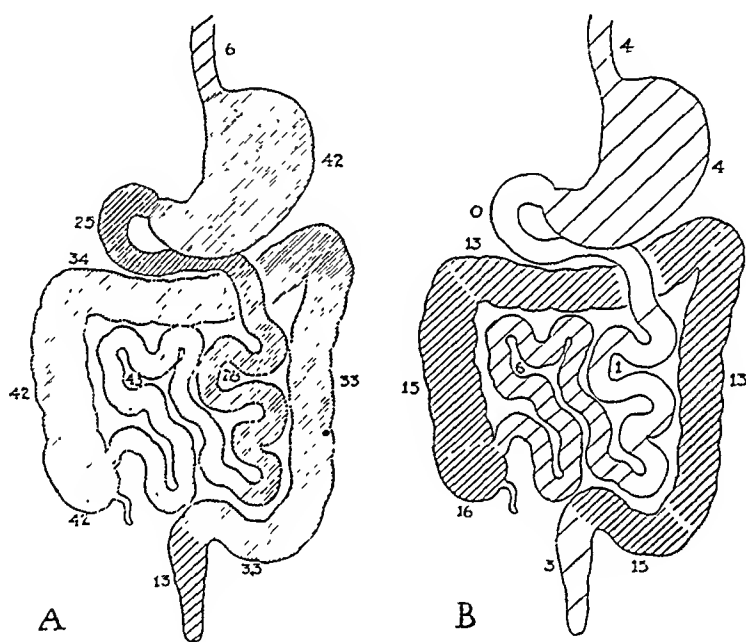


Fig. 1.—*A* shows the frequency of hemorrhages; *B*, the frequency of diphtheritic ulcerative changes in different parts of the intestinal tract. The figures refer to the number of cases.

3 cases the lower one third or one fourth of the esophagus was covered with an adherent, dirty grayish-brown and soft membrane which rested on a dark red hemorrhagic tissue. In 1 case the esophagus showed an irregular ulcer 4 by 3 cm. in diameter which was located just above the cardia. The floor of this ulcer was formed by a dirty grayish-brown material. In the group with uremic lesions of the stomach we do not include 1 case with an acute peptic ulcer and 3 cases with typical hemorrhagic erosions. We observed 1 instance of pseudomembranous gastritis. In the midportion of the lesser curvature for a distance of 3 cm. the mucosa of the stomach was transformed into an adherent, yellowish-gray membrane which was about 1 mm. thick and was sur-

rounded by a purplish-red zone. In the 3 other cases multiple small and shallow ulcers with sharp edges and a grayish-brown floor were found scattered in the fundus and prepyloric region.

In the intestine the changes were so pleomorphic that it would require much space to describe them in detail. They always showed intimate relations to hemorrhages and varied from a single raised necrotic plaque or a single ulcer a few millimeters in diameter to extensive dirty grayish-brown or greenish-brown membranes and large confluent ulcers. The ulcers were irregular with geographic outlines and indented edges that were not undermined. The floor was formed by the submucosa or muscularis propria and was usually covered with friable remnants of necrotic material. In the colon the ulcers occupied the height of the transverse and longitudinal folds. Ulcers and diphtheritic membranes were sometimes combined, and the picture was then indistinguishable from an acute bacillary dysentery. In 3 instances the ulcers of the intestine were associated with an early fibrinous peritonitis.

It is interesting to note that the duodenum was never affected by the pseudomembranous and ulcerative processes and that there was only 1 case of ulcerative jejunitis. In the French literature reference is occasionally made to a uremic ulcerative duodenitis, but Siegmund suggested that the lesions observed by the French authors were probably simple hemorrhagic erosions.

In the cases with the dysentery-like changes the content of the colon was liquid, often bloody, mixed with shreds of necrotic tissue and of offensive odor. The clinical picture was dominated by profuse and uncontrollable diarrhea. When only a few necrotic plaques or single ulcers were present, the intestinal symptoms were often less outspoken, and in some cases they were so slight that they did not attract the clinician's attention and were overshadowed by the nervous, respiratory and circulatory manifestations. Virchow made the statement that intestinal ulcerations may not cause diarrhea. The edematous and simple hemorrhagic changes in the intestine were sometimes found associated with persistent constipation. The variability of the intestinal symptoms in uremia has been stressed by Barrillon¹⁸ and many others. According to Blanchet,¹⁹ uremia is accompanied by diarrhea as often as by constipation. Volhard says that in rare instances the clinical and anatomic picture of uremia may closely resemble that of true dysentery. In reviewing the intestinal symptoms of 307 cases of chronic Bright's disease Fischer found diarrhea 84 times and constipation 45 times. Of 26 cases of uremia, 16 showed severe diarrhea.

18. Barrillon, Maurice: Contribution à l'étude de l'urémie digestive, Thèse de Paris, no. 68, 1897.

19. Blanchet, R.: Contribution à l'étude de l'urémie gastro-intestinale, l'urémie occlusive, Thèse de Paris, 1911.

Since pseudomembranous and ulcerative lesions of the gastrointestinal tract in uremia are of grave significance, their early recognition is of great importance. This early recognition, however, is often rendered difficult because of the absence of characteristic symptoms. Anatomic observations suggest that the microscopic and chemical demonstration of blood in the feces should prove a valuable sign of the imminent danger of severe gastro-intestinal complications.

A question arises as to the relations between the type of renal lesion that causes the uremia and the intensity of the gastro-intestinal changes. Pseudomembranous and ulcerative processes were encountered most frequently in cases of uremia due to pyelonephritis (40 per cent), but since there were only 5 cases of pyelonephritis with uremia in our material the number is too small to permit us to draw any definite conclusions. Acute glomerulonephritis was second in frequency with 30.2 per cent. Subacute glomerulonephritis followed next with 23.0 per cent and chronic glomerulonephritis with 19.3 per cent. For malignant nephrosclerosis the corresponding figure was 16.6 per cent. It seems, therefore, that glomerulonephritis leads more frequently to necrosis and ulceration in the digestive tract than the vascular form of renal insufficiency. Further studies on a larger amount of material are necessary to show whether this statement is correct.

MICROSCOPIC OBSERVATIONS

In the mild forms of uremic intestinal changes histologic examination reveals a thickening of the submucosa and a dilatation of the veins of the basal venous plexus of the mucosa and especially of the submucosa. The thickening of the submucosa is due to an edematous loosening of the ground substance and, in many instances, also to an actual increase in connective tissue fibers. The crypts of the mucosa are dilated and filled with mucus and desquamated and degenerated epithelial cells. With the onset of the hemorrhages the congestion of the venules and veins becomes most marked, and there is an extreme stasis in the capillaries of the mucosa (fig. 2). In the veins of the submucosa the red cells are often so densely packed together that they form solid casts (fig. 3). The first hemorrhages appear in the basal parts of the mucosa and spread gradually to the inner surface. In the severe forms there is a complete hemorrhagic infarction of the mucosa. The crypts are filled with cellular debris and red blood cells, and the edema is most striking in the submucosa. In the stage of hemorrhagic infarction of the mucosa the venules of the submucosa show peripheral accumulation of the leukocytes and also leukodiapedesis (fig. 4). Proliferation of the local histiocytes and filling of the lymph vessels with

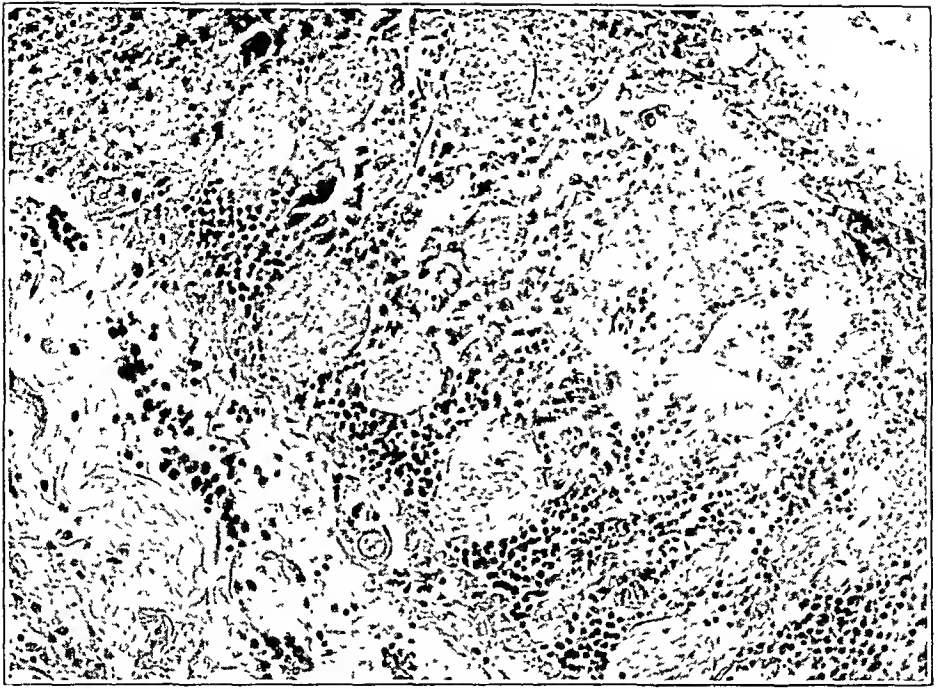


Fig. 2.—Section of the lower ileum showing marked engorgement of the deep venous plexus of the mucosa and numerous hemorrhages above the dilated venules. The submucosa is edematous. There is an increase in the number of local histiocytes with an accumulation of mononuclear cells in the lymph vessels. The patient was a colored man, aged 38, suffering from chronic glomerulonephritis with focal areas of cortical necrosis. The duration of the uremic symptoms was three weeks. Reduced from a magnification of $\times 300$.



Fig. 3.—Section of the ascending colon illustrating the enormous dilatation of the veins of the submucosa. The patient was a white man, aged 44, with chronic glomerulonephritis. The duration of the uremic symptoms was one month. Reduced from a magnification of $\times 300$.



Fig. 4.—Section of cecum. Note the hemorrhagic infarction of the mucosa and the enormous edema of the submucosa. The venules in the submucosa show a peripheral arrangement of the leukocytes and leukodiapedesis. The patient was a white man, aged 50, with subacute glomerulonephritis. The duration of uremic symptoms was three weeks. Reduced from a magnification of $\times 150$.

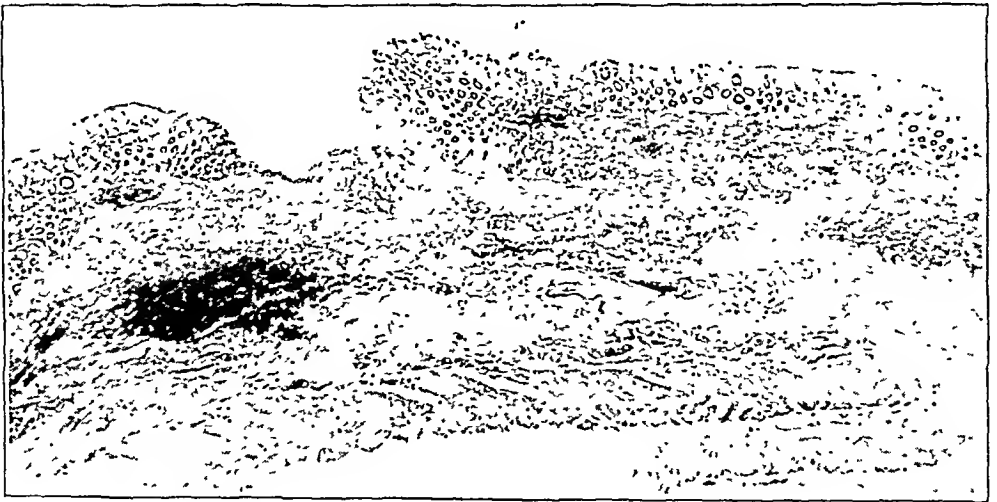


Fig. 5.—Section of the cecum showing a uremic ulcer. There are extensive hemorrhages in the floor and at the edges of the ulcer. The overhanging edge on the right side of the ulcer is an artefact due to shrinking. The patient was a colored man, aged 46, with malignant nephrosclerosis. The duration of uremic symptoms was one week. Reduced from a magnification of $\times 18$.



Fig. 6.—Necrotic arteriole surrounded by leukocytes in the submucosa. Severe pseudomembranous ileitis. A thrombosed small vein is seen near the necrotic arteriole. The mucosa above this area is completely necrotic. The patient was a white woman, aged 28, with malignant nephrosclerosis. The duration of uremic symptoms was twelve days; $\times 150$.

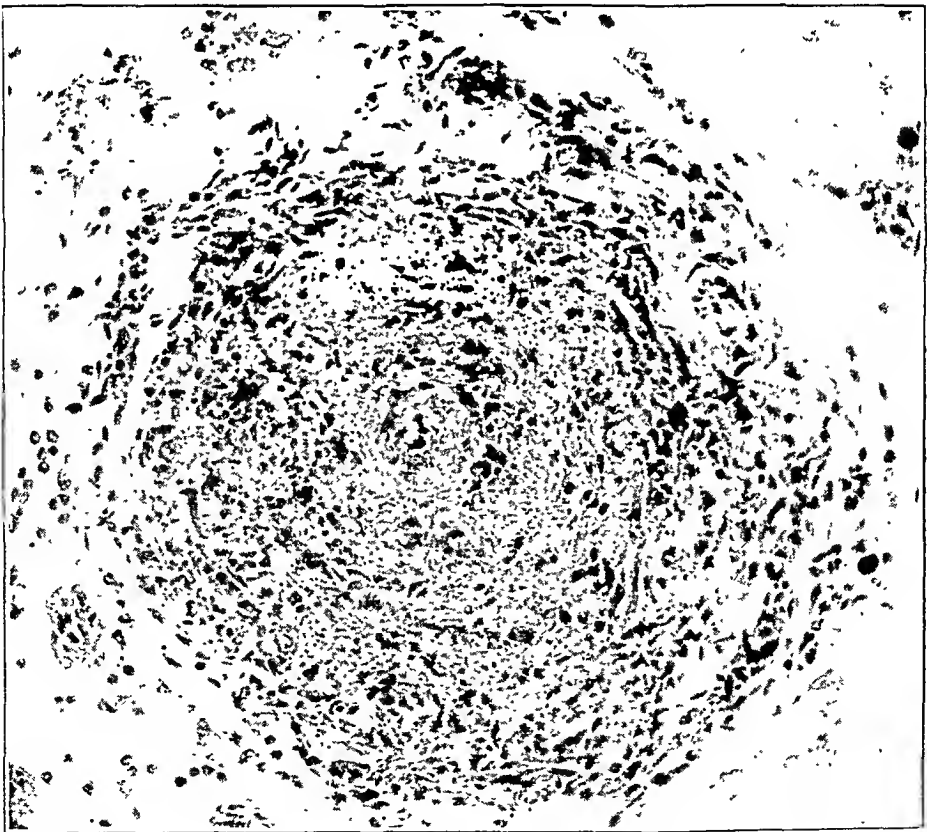


Fig. 7.—Necrotic arteriole surrounded and infiltrated by leukocytes in the submucosa of the ileum. The mucosa was necrotic, and the necrosis extended close to the arteriole. The patient was a colored man, aged 38, with chronic glomerulonephritis. The duration of uremic symptoms was two and one-half weeks; reduced from a magnification of $\times 500$.

mononuclear cells add to the increased cellularity of the submucosa. On the free surface there is a thin layer of blood mixed with degenerating cells, threads of fibrin and clumps of bacteria.

In the state of diphtheritic inflammation the mucosa is completely necrotic, and the necrosis often extends into the submucosa. Dense clouds of bacteria populate the inner portion of the necrotic membranes underneath which one finds extravasations of blood and a varying degree of demarcating inflammation. In some cases this demarcating inflammation is rather insignificant. The veins about the area of necrosis are often occluded by thrombi.



Fig. 8.—Arteriolar necrosis in the submucosa of the colon in a case of Flexner's dysentery. Reduced from a magnification of $\times 300$.

The uremic ulcer of the intestine (fig. 5) has sloping edges. The floor exposes a layer of fibrinoid necrotic tissue with degenerating leukocytes. Hemorrhages in the floor and at the edges of the ulcer are of particular significance and, according to our experience, are more extensive than in any other form of intestinal ulceration.

As pointed out in the introductory review of the literature, Siegmund is inclined to associate the uremic ulceration and necrosis of the intestine with arteriolar changes. It is well known that in cases of hypertension the intestine may take part in the sclerotic changes of the arterioles, although they are not as common and as marked as in the kidney (Fahr). We found no arteriolar changes in 9 of our 27 cases of diphtheritic and ulcerative inflammation of the intestine. In 13 cases there

was a distinct arteriolosclerosis, and necrosis of the arterioles and small arteries of the submucosa was present in 5 cases (figs. 6 and 7). The necrosis affected both previously sclerotic and unchanged vessels. The vascular necrosis was always in close proximity to the necrosis of the mucosa and was never encountered during the congestive or hemorrhagic stage of the lesions. Thus, it is undoubtedly secondary. In this connection it may be recalled that arteriolar necrosis of the submucosa is quite common in bacillary dysentery (fig. 8). Furthermore, the necrosis is distinctly inflammatory, as shown by the leukocytic infiltration in and about the necrotic vessels (fig. 7) and, hence, different from the bland fibrinoid necrosis of the arterioles of the kidneys in cases of malignant nephrosclerosis.

COMMENT

In our material diphtheritic and ulcerative lesions of the digestive tract were third in frequency among the pathologic-anatomic manifestations of uremia, uridrosis being first with 32.3 per cent and fibrinous pericarditis second with 30.8 per cent. It is significant that fibrinous pericarditis was less common in the patients with severe gastro-intestinal changes than it was in those showing mild changes. Fibrinous pericarditis was present in only 25.9 per cent of the patients with diphtheritic ulcerative lesions, while it was observed in 32.1 per cent of those with edema and hemorrhages, which indicates that different factors are at work in causing the pericarditis and the intestinal necrosis.

We have reviewed the theories which deal with the pathogenesis of uremic necrosis and ulceration of the digestive tract. Siegmund's explanation has already been discarded on the basis of the microscopic observations. Our observations also do not support the old and often quoted theory of Treitz which is based on the compensatory elimination of urea through the glands of the stomach and intestine. When one divides the cases of uremia into two groups, one with and one without necrotic or ulcerative lesions of the gastro-intestinal tract, one observes practically no difference in the degree of retention of urea. The general average is slightly higher in the first than in the second group, the respective figures for urea nitrogen being 137 mg. and 120 mg. per hundred cubic centimeters of blood. The range of variation, however, is about the same, namely between 50 and 250 mg., and the extremely high values (above 200) are not more common in the first than in the second group. The relatively small number of cases and the wide range of variation of the urea content of the blood do not allow a satisfactory calculation of the standard variation for the group with intestinal necrosis and ulceration. But even without exact mathematical figures it can be safely stated that there is no parallelism between the severity of the gastro-intestinal changes and the retention of urea. What has

been said of the urea also holds true for the other substances which were determined in the blood, namely, creatinine, uric acid and indican. Nor were there any differences in the decrease of the carbon dioxide-combining power of the plasma. Determinations for xanthoprotein were not made on our patients. There is an additional important factor which speaks against the theory of excretion, namely, the occurrence of diphtheritic and ulcerative lesions in the esophagus and, especially, in the vagina, the evolution of which is identical with that of the intestinal changes. While the literature refers occasionally to the involvement of the esophagus, the changes in the vagina are hardly mentioned, although they are characteristic. In 8 (13.1 per cent) of our 61 female patients with uremia a diphtheritic or ulcerative colpitis was recorded. Many of the remaining 53 cases showed discrete or confluent hemorrhages in the vaginal mucosa. So far as the hypertension theory of Bensaude and Lemierre is concerned, an exceedingly high blood pressure did not seem to favor the development of pseudomembranes or ulcers.

Comparing the two schematic drawings in figure 1 which depict the frequency of the hemorrhages and diphtheritic and ulcerative changes, respectively, in the lower part of the esophagus, stomach and intestine, one observes an important difference. While the hemorrhages are equally common in the stomach, ileum and colon and are also frequently encountered in the duodenum and jejunum, the severe lesions reveal a distinct predilection for the ileum and colon. In other words, necrosis and ulceration occur chiefly where the intestinal content is rich in bacteria. The hemorrhagic areas of the esophagus become infected by the bacteria which are swallowed with the food, mechanical factors determining the selection of the lowermost portion. Mechanical factors are also instrumental in disposing the region of the ileocecal valve to necrosis and ulceration. There was only 1 instance of pseudomembranous inflammation in the stomach. The ulcers in the other 3 cases were somewhat different from typical hemorrhagic erosions, but since they were sharply punched out, they too were most likely peptic.

We believe, therefore, that the uremic necrosis and ulceration of the intestine are secondary to hemorrhages, as Mathieu and Roux suggested many years ago. The hemorrhages loosen the epithelial cover of the mucous membranes and decrease the vitality of the tissue. Where present, bacteria infect the hemorrhagic tissue, causing necrosis and ulceration. There is no indication for the elimination of chemical substances so strong as to produce necrosis. The hemorrhages in the digestive tract are a part of the hemorrhagic diathesis which is common in uremia and which leads to hemorrhages in many other organs, as for instance in the epicardium, lung, mucosa of the renal pelvis, urinary bladder,

uterus and vagina. Six of our patients showed so many petechiae of the skin that the diagnosis on admission suggested a blood dyscrasia. Morawitz²⁰ explained the hemorrhagic diathesis in uremia on the basis of the autointoxication. We do not know what substance acts on the vessels to make them permeable for the blood cells. Nor are we able to decide definitely whether this substance affects the vessels directly or indirectly by way of the vasomotor nerves in the sense of Ricker. The latter explanation appears to us more likely, since no anatomic alterations of the wall of the capillaries or small veins could be detected, and the extreme dilatation of the capillaries and small veins was in striking contrast to the narrow arterioles and small arteries. Thus, the histologic observations suggest that, similar to the chief manifestations of the acute eclamptic and chronic pseudo-uremia, the intestinal lesions of true uremia are the result of disturbances in the innervation of the terminal vascular bed. In the two forms of pseudo-uremia these disturbances affect mainly the central nervous system, leading to edema, focal rarefaction of the ganglion cells and, eventually, softening and hemorrhages. In true uremia they are more generalized, causing hemorrhages in many organs of the body (esophagus, ileum, colon and vagina), which, in the presence of bacteria, are followed by necrosis and ulceration.

SUMMARY

The study deals with the pathologic-anatomic changes of the digestive tract in uremia. The diphtheritic ulcerative processes which were encountered in 19.8 per cent of the 136 cases could be traced to localized circulatory disturbances. The earliest changes consist of capillary hyperemia of the mucosa, increased production of mucus and dilatation of the small veins of the submucosa. The increased permeability which is associated with the extreme widening of the small blood vessels leads first to edema and later to hemorrhages. Bacteria from the intestinal content settle in the devitalized hemorrhagic areas of the mucosa of the intestine and cause fibrinous exudation and necrosis. The necrotic parts are sequestered, and ulcers are formed.

Attention is called to the occurrence of a pseudomembranous ulcerative colitis in uremia, the pathogenesis of which is identical with that of the intestinal lesions.

20. Morawitz, P.: *Verhandl. d. deutsch. path. Gesellsch.* **25**:32, 1930.

EFFECT OF ARTERIOSCLEROSIS AND BENIGN AND MALIGNANT HYPERTENSION ON THE AREA OF HISTAMINE FLARES

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AND

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The syndrome of malignant hypertension, as described by Keith and his associates,¹ is characterized by severe arterial hypertension, neuroretinitis, a progressive course and a uniformly poor prognosis. The condition usually represents the final stage of benign essential hypertension, but occasionally appears to be of the malignant type from the onset. The neuroretinitis varies in severity from mild to extreme in different cases and in all but the final stage is characterized by the invariable presence of edema of the disks, with edema of the surrounding retina. This feature is often out of proportion to the other retinal changes, such as hemorrhagic areas, cotton-wool exudates and sclerosis of the retinal arteries. Renal function frequently is normal or only slightly reduced at the time the condition is first recognized. The erythrocyte count and hemoglobin content of the blood are seldom more than slightly diminished. Death usually occurs within two years after the diagnosis is made and may be result of cerebral hemorrhage, congestive myocardial failure, renal insufficiency or a combination of these causes.

The differentiation of typical cases of benign and malignant hypertension is comparatively simple and is based primarily on the results of ophthalmoscopic examination. There is a group of cases, however, which cannot be placed in either the benign or the malignant class. Ophthalmoscopic examination reveals more extensive changes, in the form of retinal sclerosis, exudates and hemorrhagic areas, than are present in patients with benign hypertension, and yet, because of the absence of edema of the disks, the condition cannot be classified as malignant hypertension. Some of these undoubtedly are cases of early malignant hypertension, while others represent severe grades of the benign form. In the present study these cases have been grouped together and labeled

From the Cleveland Clinic.

1. (a) Wagoner, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *Arch. Int. Med.* **34**:374 (Sept.) 1924.
(b) Keith, N. M.; Wagoner, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, *ibid.* **41**:141 (Feb.) 1928.

hypertension of intermediate grade. Kernohan, Anderson and Keith² employed a similar classification.

Pathologic studies of the arterioles of voluntary muscle obtained at biopsy and of the arterioles of various organs at necropsy were made by Kernohan, Anderson and Keith² in patients with hypertension of the benign, intermediate and malignant types. They observed that in benign hypertension the arterioles may be entirely normal or may show moderate lesions, while in the intermediate and malignant types more advanced changes are the rule. The lesions consist of hypertrophy of the media, proliferation of the intima and marked reduction in the ratio of the wall to the lumen. The character and widespread distribution of these changes in the arterioles and the probability that the arterioles are also in a state of greatly increased tone³ suggested that patients with hypertension of the intermediate and malignant types might show alterations in the response of the cutaneous vessels to histamine.

Sir Thomas Lewis⁴ observed that when a solution of histamine acid phosphate is placed on the skin of normal persons and punctured into the epidermis with a fine needle, the ensuing reaction consists of three distinct phases. There first appears a reddish-purple spot about the site of the puncture. This is surrounded within a minute or less by a bright flare, and finally, the original reddish-purple spot is covered by a wheal. The entire reaction reaches its maximum development in from three to five minutes. After extensive studies Lewis concluded that the purplish spot about the site of puncture results from local dilatation of the minute vessels of the skin (terminal arterioles, capillaries, collecting venules and subpapillary venous plexus), and that the wheal is due to increased permeability of the walls of these vessels. The flare, on the other hand, is the result of widespread dilatation of the neighboring strong arterioles (arched arterioles), and is brought about through a local nerve reflex (axon reflex). Dilatation of the strong arterioles causes passive engorgement of the minute vessels of the skin, and it is to the congestion of these vessels that the arterial color of the histamine flare is due.

The available evidence cited earlier indicates the presence of a disturbed state of the arterioles in patients with essential hypertension. As the flare is more directly related to the condition of the arterioles than are the other two phases of the histamine reaction, it seemed probable that if different grades of essential hypertension produced quantitative

2. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**:395 (Sept.) 1929.

3. Volhard, F.: *Der arterielle Hochdruck*, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.

4. Lewis, T.: *The Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, Ltd., 1927.

differences in the response to histamine, the alterations could be detected best by observations on the area of the flare. Actual measurements of the area of histamine flares do not appear to have been made, and for this reason control observations in normal persons were necessary. In addition, because earlier investigators⁵ recorded delayed or reduced responses to histamine in patients with arteriosclerosis, it seemed desirable to include in the present study measurements of the area of the flare in patients with arteriosclerosis and normal blood pressure.

METHODS OF STUDY

The technic of puncturing the skin through a drop of histamine solution was discarded in favor of the intradermal injection of a measured amount of the drug. With the latter procedure larger flares may be obtained, and these flares, as a rule, are less variable in size than are those produced by the puncture method. All observations were made at ordinary room temperature, with the patient in the recumbent position and with the arms supported at the level of the right auricle. The skin of the flexor surface of the midforearm was swabbed gently with alcohol and allowed to dry. Approximately 0.02 cc. of a 1:2,000 solution of histamine dihydrochloride containing 0.5 per cent of chlorbutanol as a preservative was then injected into the superficial layers of the skin with a tuberculin syringe and a 26 gage hypodermic needle. The development of the flare was observed carefully, and at the end of five minutes or as soon thereafter as the reaction was complete the borders of the flare were outlined with ink and traced on thin copy paper. The intensity of the color was noted. The surface area of the flare was measured subsequently by retracing the outline from the copy paper to thin lead foil of uniform thickness and uniform weight per square centimeter. The pattern on the foil was cut out and weighed, and the area of the flare was calculated from the known weight of the foil per unit of area.

Observations were made on both forearms in each patient studied, and, in approximately one half of the persons the test was repeated on one or more occasions. In each subject the average of all measurements on both forearms was taken as the final area of the flare. On rare occasions, and apparently as the result of the escape of the histamine solution into the lymphatic system of the skin, wheals were formed with long projecting tongues instead of the usual fairly regular outline. These wheals were accompanied by abnormally large flares, and because the form of the wheals indicated an abnormal distribution of the stimulus, reactions of this kind were not included in computing the results.

All persons subjected to the test had a normal oral temperature at the time the observations were made, and none presented evidence of congestive myocardial failure. Routine blood counts and urinalyses were made in all subjects, and in the patients with hypertension the renal function was measured by the urea clearance

5. Starr, I., Jr.: Studies on the Circulation of the Feet in Diabetes Mellitus With and Without Gangrene, *Am. J. M. Sc.* **180**:149, 1930. Caldwell, J. M., Jr., and Mayo, J. G.: Cutaneous Reactions to Histamine: Reactions in Occlusive and Spastic Vascular Disease and in Chronic Infectious Arthritis, *Arch. Int. Med.* **47**: 403 (March) 1931. de Takáts, G.: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, *ibid.* **48**:769 (Nov.) 1931.

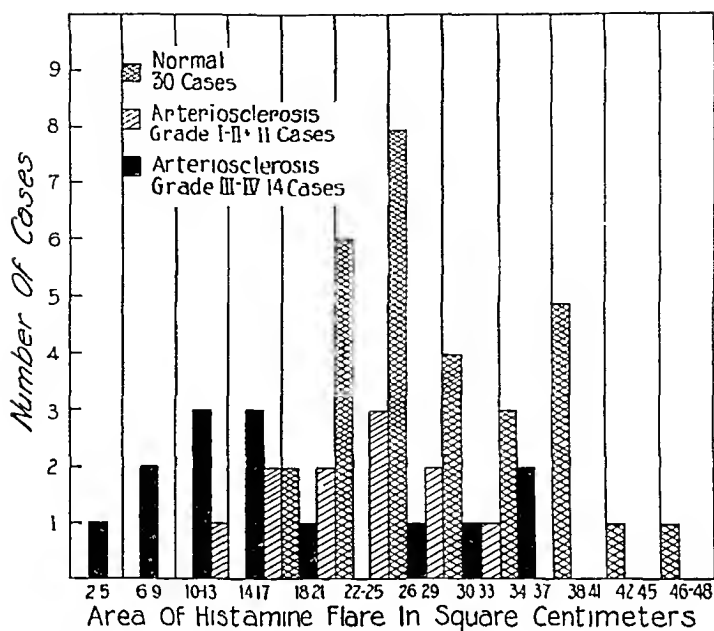


Chart 1.—Comparative distribution of the areas of the histamine flare in normal persons and in patients with arteriosclerosis and normal blood pressure.

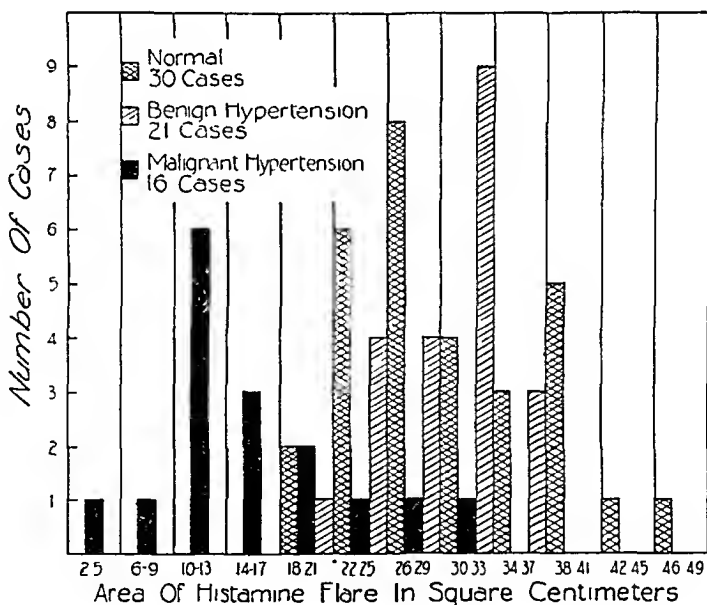


Chart 2.—Comparative distribution of the areas of the histamine flare in normal persons and in patients with benign and malignant hypertension.

test.⁶ Care was exercised to exclude possible instances of chronic glomerulonephritis from the series of cases of benign, intermediate and malignant hypertension.

RESULTS

The area of the flare produced by the intradermal injection of histamine was measured in five groups: (1) thirty normal persons, (2) twenty-five patients with arteriosclerosis and normal blood pressure, (3) twenty-one patients with essential hypertension of the benign type, (4) eleven patients with hypertension of the intermediate grade and (5) sixteen patients with malignant hypertension.

Normal Conditions.—The normal persons were between 18 and 58 years of age. The blood pressure was within the limits of normal in all, and in none was there palpable thickening of the radial or brachial arteries. The area of the histamine flare ranged from 18 to 48 sq. cm., with an average value of 31 sq. cm. An area of less than 25 sq. cm. was recorded in only six instances. In several persons there was a considerable variation in the area of the flare on the two forearms and in the size on the same arm at different times. In no instance, however, was an abnormally small flare observed.

Arteriosclerosis and Normal Blood Pressure.—Eleven patients between the ages of 48 and 75 years had slight or moderate peripheral arteriosclerosis and normal blood pressure. In none of these did the history or physical findings, including the results of ophthalmoscopic examination, suggest that hypertension had been present in the past. The color of the histamine flare was normal in all instances but one. There was a tendency, however, toward a slight diminution in the size of the flare. The area was less than 25 sq. cm. in seven of the eleven patients, but in only three was it smaller than the smallest recorded in a normal person. The average area for the entire group was 22 sq. cm.

Fourteen patients between the ages of 50 and 80 years had advanced arteriosclerosis and normal blood pressure. None presented evidence of having had hypertension in the past. The color of the histamine flare was paler than normal in five. Although the area varied in different persons from 3 to 36 sq. cm., a distinctly greater tendency toward flares of reduced size was observed than in the group with lesser degrees of arteriosclerosis. In nine of the fourteen patients the flare was smaller than the smallest recorded in a normal person. The average area for the entire group was 18 sq. cm.

Benign Hypertension.—The twenty-one patients with essential hypertension of the benign type were between the ages of 29 and 67

6. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation 6:427 (Dec.) 1928.

TABLE 1.—*Observations on Patients with Benign Hypertension*

No.	Age, Years	Sex	Blood Pressure		Duration of Hyper- tension, Years	Peripheral Arterio- sclerosis, Retin- itis	Fundus		Blood		Urine			Histamine Tlaxer			
			Sys- tolic, Mm. Hg	Diastolic, Mm. Hg			Sclerosis	Erythro-globin, Millions Cent	Hemo- cytes, per Cent	Urea, Mg.	Specific Gravity	Albu- min	Casts	Urea Clearance, per Cent	Color	Area, Sq. Cm.	
1	50	F	174	104	4+	0	0	Slight	5.6	84	24	1.022	0	0	145	Normal	30
2	54	M	170	106	Unknown	II	0	Slight	4.8	88	30	1.020	Trace	0	41	Normal	32
3	61	F	182	100	10+	II	0	Advanced	4.7	84	42	1.017	Trace	0	40	Normal	27
4	59	M	180	104	3	I	0	Moderate	5.0	104	30	1.020	0	0	41	Normal	31
5	29	F	170	110	4	0	0	Slight	4.8	87	30	1.020	Trace	0	81	Normal	26
6	63	M	230	124	5+	II	0	Slight	4.2	65	33	1.017	0	+	..	Normal	31
7	49	F	210	110	12+	I	0	Slight	4.5	60	27	1.026	Trace	0	72	Normal	20
8	38	F	196	126	12+	0	0	Slight	4.4	85	24	1.022	0	0	66	Normal	30
9	49	F	210	118	4-	I	H.*	Slight	4.6	80	30	1.020	Trace	+	76	Normal	35
10	55	F	184	94	Unknown	I	0	Slight	4.2	71	36	1.027	Trace	0	65	Normal	25
11	55	M	200	106	Unknown	I	0	Slight	5.1	97	..	1.024	0	0	..	Normal	22
12	58	M	160	96	7+	III	0	Slight	5.1	91	45	1.023	Trace	+	78	Normal	28
13	49	F	210	110	6+	II	0	Moderate	4.8	84	33	1.021	0	0	45	Normal	35
14	42	M	206	106	Unknown	II	0	Slight	4.0	61	42	1.030	0	0	69	Vivid	36
15	53	M	196	112	Unknown	II	H.*	Moderately advanced	4.9	84	24	1.022	Trace	0	141	Pale	32
16	45	F	196	116	4+	II	0	Slight	4.8	90	39	1.018	0	0	59	Normal	33
17	52	F	230	110	8+	I	0	Moderate	5.0	85	36	1.026	Trace	0	85	Pale	26
18	40	F	220	110	Unknown	I	0	Moderate	4.1	84	42	1.012	0	0	43	Normal	23
19	67	F	190	100	6-	I	0	Moderate	4.6	78	24	1.030	0	0	65	Normal	24
20	56	M	180	116	Unknown	II	0	Moderate	5.1	91	28	1.021	0	0	72	Normal	30
21	42	F	230	126	Unknown	I	0	Advanced	4.8	91	30	1.020	0	0	100	Normal	31
Average	51		196	110					4.7	83	32				73		29

* Few small hemorrhages.

years. The average blood pressure was 196 systolic and 100 diastolic. The duration of the hypertension in the patients in whom it could be estimated ranged from three to more than twelve years. Slight or moderate peripheral arteriosclerosis was usually present. Ophthalmoscopic examination revealed from slight to advanced sclerosis of the retinal vessels, but in no instance was there retinitis or papilledema. The color of the histamine flare was diminished in only two instances. The area of the flare was within the limits of normal in all, and the average area for the group was 29 sq. cm. A summary of the observations on patients with benign hypertension is presented in table 1.

Hypertension of the Intermediate Grade.—The eleven patients with essential hypertension of the intermediate grade were between the ages of 34 and 62 years. The average blood pressure was 210 systolic and 120 diastolic. The duration of the hypertension in the patients in whom it could be estimated varied from approximately one to eighteen years. From slight to moderately advanced peripheral arteriosclerosis was present in all. Ophthalmoscopic examination revealed from moderate to advanced sclerosis of the retinal vessels and from slight to advanced degrees of retinitis. In four patients the outline of the optic disks was hazy, but actual papilledema was not present. The color of the histamine flare was diminished in only two instances, but a well defined tendency toward reduction in area was observed. In only two of the eleven patients did the area exceed 25 sq. cm., while in four the flare was smaller than the smallest recorded in a normal subject. The average area for the entire group was 20 sq. cm. A summary of the observations is presented in table 2.

Malignant Hypertension.—The sixteen patients with malignant hypertension were between the ages of 26 and 66 years. The average blood pressure was 225 systolic and 130 diastolic. The duration of the hypertension in the patients in whom it could be estimated ranged from less than three years to eight years. A certain degree of peripheral arteriosclerosis was present in all the patients, but in only three was this of advanced grade. Edema of the optic disks and of the surrounding retina was present in all but one patient, in whom there was an extensive bilateral vitreous hemorrhage obscuring the disks. Exudates and hemorrhagic areas were noted in fourteen of the sixteen patients, but in many these changes were slight in comparison with the degree of neuroretinal edema. Sclerosis of the retinal vessels was an invariable finding, and usually was of moderate or advanced grade. Abnormally pale histamine flares were obtained in seven of the sixteen patients in this group. In eleven patients the area of the flare was less than the smallest observed in a normal subject, while in only three did it exceed 24 sq. cm. The average area for the entire group was 16 sq. cm., approximately

TABLE 2.—*Observations on Patients with Essential Hypertension of Intermediate Grade*

No.	Age, Years	Sex	Blood Pressure		Duration Peripheral of Hyper-Arterio-tension, selerosis, Years	Grade	Fundus		Blood		Urine		Histamine Tissue			
			Sys-tolic, Mm. Hg	Diastolic, Mm. Hg			Retin-itis	Selerosis	Erythro-globin, per Millions	Hemo-cent	Urea, Mg.	Specific Gravity	Albu-min	Cast- s	Urea Clearance, per Cent	Color
1	55	F	230	120	3	I+	Slight	Moderately advanced	5.0	91	42	1.009	0	0	Normal	21
2	34	M	150	106	1½	II	Slight	Moderately advanced	5.1	91	39	1.015	0	0	Pale	20
3	53	F	220	112	Unknown	II+	Slight	Advanced	4.6	91	45	1.019	Trace	0	Normal	16
4	53	F	210	120	18	I	Slight	Moderate	4.5	84	33	1.008	Trace	0	Vivid	14
5	50	F	220	110	5	I	Moderately advanced	Moderately advanced	4.4	84	30	1.020	Trace	0	Normal	33
6	62	M	204	114	3+	III+	Slight	Advanced	4.6	97	45	1.023	Trace	0	Normal	20
7	58	M	200	120	Unknown	II	Moderately advanced*	Moderately advanced	4.9	81	45	1.025	Trace	+	Normal	26
8	46	F	180	98	1+	I	Slight*	Advanced	4.6	81	54	1.012	Trace	0	Normal	22
9	61	M	256	160	10+	III+	Slight*	Advanced	4.0	74	75	1.020	+	++	Pale	13
10	50	M	264	150	10+	II+	Moderate*	Moderately advanced	6.1	-97	27	1.020	Trace	+	Normal	25
11	54	F	180	108	10	II	Advanced	Advanced	4.7	78	39	1.026	Trace	0	Normal	15
Average 53			210	120	4.8	86	43	20

* Including haziness of the optic disks.

TABLE 3.—*Observations on Patients with Malignant Hypertension*

No.	Age, Years	Sex	Blood Pressure		Duration of Hyper-tension, Years	Peripheral Arterio-sclerosis, Grade	Fundus*		Blood		Urine			Histamine Flare			
			Sys- tole, Mm. Hg	Diastolic, Mm. Hg			Retin- itis	Sclerosis	Erythro- cytes, Millions	Hemo- globin, Cent	Urea, Mg.	Specific Gravity	Albu- min	Casts	Urea Clearance, per Cent	Color	Area, Sq. Cm.
1	45	F	280	110	5+	III	Moderate	Advanced	6.2	97	45	1.022	Trace	++	35	Vivid	30
2	52	M	210	140	4	IV	Advanced	Advanced	4.4	84	111	1.014	++	++	16	Normal	12
3	34	M	206	130	3—	I	Moderately advanced	Advanced	4.4	84	39	1.013	Trace	+	89	Pale	18
4	66	M	200	110	Unknown	II+	Slight	Advanced	5.0	91	36	1.020	Trace	+	87	Normal	7
5	51	M	280	110	4	II+	Slight	Moderately advanced	5.1	91	40	1.025	Trace	++	57	Normal	5
6	48	M	300	166	Unknown	II+	Advanced	Advanced	4.3	71	66	1.018	+++	0	48	Pale	12
7	55	F	190	120	Unknown	I	Advanced	Moderate	4.1	75	36	1.010	Trace	0	64	Pale	10
8	44	F	250	170	1½+	II	Hemorrhage†	Hemorrhage†	4.0	70	45	1.013	++	++	19	Pale	19
9	40	F	220	160	3—	I+	Advanced	Moderately advanced	4.8	74	27	1.013	Trace	0	49	Pale	17
10	54	F	190	110	Unknown	I	Slight	Moderate	5.3	91	36	1.020	0	0	98	Normal	12
11	47	F	216	123	5+	I+	Advanced	Moderate	4.4	78	36	1.020	Trace	0	50	Normal	17
12	43	F	260	150	8	III	Moderate	Moderate	4.2	85	39	1.013	0	0	53	Pale	13
13	49	M	180	96	5	I	Moderate	Moderate	4.6	85	45	1.012	0	0	61	Normal	27
14	32	F	214	124	5+	I+	Slight	Moderate	4.9	79	36	1.018	Trace	+	55	Pale	12
15	27	F	240	140	3	I	Advanced	Advanced	4.2	71	30	1.019	Trace	0	55	Normal	17
16	26	F	170	110	4	I	Slight	Slight	4.6†	78	39	1.024	0	0	49	Normal	25
Average	45		225	130	4.7	82	44	55	16

* Neuroretinal edema present in all cases.

† Extensive bilateral vitreous hemorrhage.

one half of the average in normal persons. A summary of the observations is presented in table 3.

As a general rule the variations in the area of the flares on the two forearms and in the size of the flares on the same arm at different times were of smaller magnitude in patients with arteriosclerosis or hypertension than in normal persons. This was particularly true in those with flares of low normal or definitely reduced area.

The frequency distribution of the areas of the flares in normal persons and in the patients with arteriosclerosis, benign hypertension and malignant hypertension is presented in charts 1 and 2. The average values for age, blood pressure and area of the flare in all groups of patients are given in table 4.

TABLE 4.—*Table of Average Values*

Condition	Number of Cases	Age, Years	Blood Pressure		Area of Histamine Flare, Sq. Cm.
			Systolic, Mm. Hg	Diastolic, Mm. Hg	
Normal	30	35	118	73	31
Arteriosclerosis, grades I and II.....	11	65	133	73	22
Arteriosclerosis, grades III and IV.....	14	68	131	72	18
Benign hypertension	21	51	196	110	29
Hypertension of intermediate grade...	11	53	210	120	20
Malignant hypertension	16	45	225	130	16

COMMENT

The results of the present investigation demonstrate that in patients with advanced arteriosclerosis and in those with essential hypertension of the intermediate and malignant types the area of the flare produced by the intradermal injection of histamine usually is diminished. A tendency toward flares of reduced size is observed in patients with normal blood pressure and slight or moderate degrees of arteriosclerosis, although the area is usually within the lower range of normal. Patients with essential hypertension of the benign type have flares of normal area, even though arteriosclerosis also is present.

Under the conditions of the present study diminution in the area of the histamine flare may result from: (1) an interruption of the pathway of the axon reflex through which the stimulus for dilation reaches the strong arterioles of the skin, (2) a reduction in the amount of available blood that can flow into the dilated strong arterioles and through them into the minute vessels of the skin and (3) anatomic or functional changes in the strong arterioles or in the minute vessels which interfere with the normal dilatation of these vessels. There is at present no method available by means of which one may test the functional integrity of the axon reflex alone. It is not probable, however, that a disturbance of the nerve pathways is the primary factor responsible for

the diminished flares in patients with arteriosclerosis or hypertension of the intermediate and malignant types.

The arterioles in patients with senile arteriosclerosis may show slight fatty degeneration in the media, but no other changes are present.⁷ It is not probable that such minor alterations are responsible for the diminished histamine flares in these patients. There is also no evidence of an abnormal degree of arteriolar contraction in arteriosclerosis. The most logical explanation of the occurrence of reduced flares in patients with arteriosclerosis and normal blood pressure, therefore, would seem to be that the arteriosclerotic changes in the large and small arteries are accompanied by a reduction in the blood flow of sufficient magnitude to interfere with the full development of the flare.

The observations on the patients with benign hypertension are of considerable significance. The occurrence of flares of normal size in these patients in the presence of various degrees of arteriosclerosis indicates that the factor responsible for the reduced flares in persons with arteriosclerosis and normal blood pressure is not of importance in the presence of hypertension. It follows, therefore, that the diminution in the area of the histamine flare observed in patients with intermediate and malignant hypertension cannot be attributed to the accompanying arteriosclerosis. The degrees of arteriosclerosis were approximately the same in the patients with intermediate or malignant hypertension as in those with benign hypertension. It is not probable that similar changes in the larger vessels exert a different effect in different types or degrees of hypertension.

The characteristic feature of the pathologic process of the intermediate and malignant types of hypertension is widespread hypertrophy of the media and proliferation of the intima of the arterioles.⁸ These changes have been observed in practically all the organs and tissues of the body. Relatively few observations have been made, however, on the arterioles of the skin. Fishberg⁹ found no changes in the cutaneous arterioles in seventeen cases of essential hypertension, and Watanabe¹⁰ observed thickening of the small arterioles of the skin in only six of one hundred and sixteen cases. Fahr,¹¹ on the other hand, reported

7. Evans, G.: A Contribution to the Study of Arteriosclerosis, with Special Reference to Its Relation to Chronic Renal Disease, *Quart. J. Med.* **14**:215, 1921. Keith, Wagener and Kernohan.^{1b}

8. Keith, Wagener and Kernohan,^{1b} Kernohan, Anderson and Keith.²

9. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, *Arch. Int. Med.* **35**:650 (May) 1925.

10. Watanabe, S.: Ueber die Arteriosklerose der Hautgefäße, *Schweiz. med. Wchnschr.* **51**:780, 1921.

11. Fahr, T.: Ueber die Beziehungen von Arteriolenklerose, Hypertonie und Herzhypertrophie, *Virchows Arch. f. path. Anat.* **239**:41, 1922.

that the media of the cutaneous arterioles frequently is well developed in both benign and malignant hypertension, and Kinsella¹² recently made similar observations. Whether alterations of this kind are responsible for the reduction in the area of the histamine flare in patients with intermediate or malignant hypertension cannot be stated. There is considerable evidence to support the view of Volhard³ that the change from benign to malignant hypertension is due to the occurrence of generalized vasoconstriction. If the arterioles of the skin are involved in this general angiospasm it is conceivable that the increase in tone might be of such intensity that the usual histamine stimulus could no longer cause normal vasodilatation. The area of the flare, therefore, would be diminished. The reduction in the size of the flare in patients with hypertension of intermediate grade might be accounted for in the same way.

Anatomic changes in the minute vessels of the skin (terminal arterioles, capillaries, collecting venules and subpapillary venous plexus) are not present in patients with hypertension. Lewis⁴ demonstrated, however, that these vessels are capable of active variations in tone. If the tone of the minute vessels of the skin were increased sufficiently to interfere with the passive filling of these vessels, even though normal arteriolar dilatation did occur in response to histamine, this change could account for the reduced flares in malignant and intermediate hypertension. Further studies are necessary before a final decision can be made as to the relative importance of anatomic changes in the strong arterioles and alterations in the functional state of the arterioles and minute vessels of the skin in limiting the area of the flares.

The color of the flare frequently was abnormally pale in patients with advanced arteriosclerosis and normal blood pressure and in those with hypertension of the malignant type. Although no definite relationship was observed between this change and diminution in the area of the flare, it is probable that they have a common pathogenesis.

The studies of Keith and his associates⁸ established the gravity of the prognosis in patients with essential hypertension of the intermediate and malignant types. It is, therefore, of considerable importance that these types of hypertension be recognized accurately, and any procedure that will aid in their identification must be considered of value. Since the area of the histamine flare usually is diminished in patients with malignant hypertension, and with few exceptions is reduced below normal or to the lower limits of normal in the presence of hypertension of the intermediate grade, observations on the area of the flare should prove a useful adjunct in distinguishing these conditions from benign hypertension. Careful ophthalmoscopic examination is, of course, of

12. Kinsella, R. A.: Personal communication to the authors.

more fundamental diagnostic importance, but occasions may be encountered in which the ophthalmoscopic picture is misleading. For instance, the occurrence of papilledema and elevated blood pressure in a patient with an unrecognized tumor of the brain might lead one to suspect malignant hypertension. The presence of a normal histamine flare in such a patient would warn against accepting the diagnosis of malignant hypertension without further consideration. It would seem, therefore, that observations on the area of the flare produced by the intradermal injection of histamine might be included to advantage as a routine part of the clinical study of all patients with essential hypertension.

SUMMARY AND CONCLUSIONS

1. The area of the flare produced by injecting 0.02 cc. of a 1:2,000 solution of histamine dihydrochloride into the skin of the midforearm was measured in five groups: (1) normal persons, (2) patients with arteriosclerosis and normal blood pressure, (3) patients with benign essential hypertension, (4) patients with hypertension of the intermediate grade and (5) patients with malignant hypertension.

2. The average area of the flare in thirty normal persons was 31 sq. cm., and the smallest flare recorded had an area of 18 sq. cm.

3. A distinct tendency toward flares of diminished size was observed in the patients with arteriosclerosis and normal blood pressure. In eleven patients with slight or moderate degrees of arteriosclerosis the average area of the flare was 22 sq. cm., while the average area in fourteen patients with advanced arteriosclerosis was 18 sq. cm. Three patients of the first group and nine of the second had flares of smaller size than the smallest obtained in a normal person.

4. The area of the flare was within the limits of normal in all of twenty-one patients with benign essential hypertension, and the average area for the group was 29 sq. cm.

5. The average area of the flare in eleven patients with hypertension of the intermediate grade was reduced to 20 sq. cm. Four of these patients had smaller flares than the smallest observed in a normal person.

6. In eleven of sixteen patients with malignant hypertension the area of the flare was less than the smallest recorded in a normal person, while in only three did it exceed 24 sq. cm. The average area for the group was 16 sq. cm., approximately one-half the average in normal persons.

7. The results of the investigation indicate that observations on the area of the histamine flare should prove a useful adjunct in distinguishing the intermediate and malignant types of hypertension from the benign form.

TRUE NONPARASITIC CHYLURIA ASSOCIATED WITH MENSTRUATION

REPORT OF A CASE

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This case is recorded because of the rarity of the condition and because it showed a feature which has not to our knowledge been noted in cases hitherto reported, namely, the association of chyluria with menstruation.

REPORT OF CASE

The patient, a married woman, aged 28, of British nationality, first came to our attention in November, 1931, when her husband (a doctor) sought our advice because she was passing milky urine. It soon became apparent that the condition was chyluria. We interviewed the patient and obtained the following history:

Except for the common ailments of childhood she had always enjoyed excellent health. Normal menstruation commenced just before the age of 13; it was always normal. At 16, the patient began to pass milky urine for the first time; this was ascribed to a chill after bathing. For about six months the urine was almost always milky, and then, without special treatment, it became normal again. During this time the patient had occasional momentary attacks of pain and stoppage of micturition.

There was no recurrence of the trouble for nearly twelve years. The patient married in 1928 and gave birth to a child in 1930, labor pursuing a normal course; she noticed nothing unusual about the urine during pregnancy. But early in September, 1931, following a menstrual period, the urine again became milky for two or three days. This occurred after subsequent menstrual periods, at first only after each alternate period. The milky urine appeared as the menstrual flow ceased, and it continued thus for about four days. On one occasion micturition was momentarily impeded by the passage of a clot. She felt no ill effects beyond a premonitory sense of chilliness and general aching immediately before the onset of the attack. Often the urine was clear in the morning, becoming milky toward evening, especially after exercise. She did not lose weight.

Except for a short holiday in the north of France, in 1928, she had never been abroad.

Our colleague, Dr. Paige Arnold, made a roentgen examination and reported the following: Nothing abnormal could be detected in the right or left lung, heart, great vessels or mediastinum. Calcification of some of the cartilages of the ribs was apparent; in view of the age and the sex of the patient, this was an early change. Some of the lower thoracic vertebrae showed marginal processes in

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relation to the anterior surfaces of the vertebral bodies. The right and left renal shadows were of normal size and in the normal position in the peritoneal cavity. An aggregation of shadows could be observed at the level of the fourth lumbar vertebra in the right side of the peritoneal cavity. No evidence of abnormality could be observed in the pelvis.

Urography was performed according to the technic of Abrodil; no abnormality in function could be detected in either the right or the left kidney.

The patient was later examined by Prof. Wilkie and Mr. Wade at their clinic in Edinburgh, when complete cystoscopic and pyelographic examinations were carried out; unfortunately, the chyluria had ceased before the examination.

The wall of the bladder was found to be normal. The ureters were readily catheterized and normal urine was obtained from the pelvis of both kidneys.

Pyelograms made of the kidneys showed no abnormality of outline.

Laboratory Findings.—The first specimen of urine, examined on Nov. 25, 1931, showed the following features: It was creamy white, with a faint tinge of pink. On standing or centrifugation, it still remained homogeneously white and opaque, but a small amount of blood was deposited. No "skin" or clot was formed. No globules of fat were visible. The urine gave a slightly alkaline reaction to litmus. The specific gravity was 1.018.

Microscopic examination of the deposit revealed numerous red blood cells and lymphocytes, all of which appeared fresh and not autolyzed. Threads of fibrin were present; there was no pus, and no organisms were found. *Filariae* were not found. (Inoculation of the deposit into a guinea-pig gave a negative result; there was no evidence of the presence of tubercle bacilli.) When a specimen of the urine was shaken with ether, considerable clearing of the milky opacity occurred, but a flocculent precipitate was deposited, and the supernatant fluid remained opalescent. Complete extraction with ether yielded 0.56 Gm. of total ether-soluble substances per hundred cubic centimeters.

A second specimen of urine was examined on Jan. 23, 1932. To the naked eye and under the microscope the appearances were identical with those of the first specimen, though the lymphocytes were even more numerous. They were present in much greater numbers than could be accounted for by the presence of normal blood.

On this occasion the uppermost part of the centrifugated urine was examined microscopically, but no globules of fat could be detected. The reaction was alkaline; the specific gravity, 1.018. There was no dextrose.

The white precipitate which was formed on extraction with ether was composed of proteins the molecules of which were apparently loosely linked to the molecules of the fats in a colloidal suspension. The protein linked to the fats was 0.211 per cent of the total. This was composed of the globulin fraction, which was soluble in a 10 per cent solution of sodium chloride and warm water, and the albumin fraction. After these protein fractions were removed, the urine still contained the following proteins: a trace of nucleoprotein and serum albumin, coagulating at 74 C., which together composed 0.75 per cent of the total protein. There was therefore 0.961 per cent of total protein present. The total ether-soluble substances present equaled 0.99 Gm. per hundred cubic centimeters. This included neutral fat, free fatty acids, cholesterol and lecithin. Two-hundredths gram of cholesterol was isolated from 100 cc.

A third specimen of urine was examined on May 4. The blood, protein and fat were present as before; numerous lymphocytes were noted. The content of fat was not estimated.

A fourth specimen was examined on June 14. The characteristics were as before; on this occasion, 1.56 per cent of the total ether-soluble substances was present. There was more blood than in the previous specimens. The patient then volunteered the statement that before the onset of chyluria she felt a sensation of tension in the pelvis, and then "something seemed to give way" and the next urine passed was milky. She was having trouble with clots in the bladder.

A specimen of urine was examined on February 4, during the interval between the second and third examinations. It was clear and normal in appearance. There was a slightly alkaline reaction to litmus. The specific gravity was 1.016. No protein could be detected by any of the tests. There was no dextrose or fat present.

On microscopic examination the deposit showed only a little mucus and a few epithelial cells. No lymphocytes, red blood cells or casts were seen.

Examinations of the blood were made on several occasions, both during the attacks of chyluria and during the intervals between the attacks. Beyond slight secondary anemia, no abnormality was found. There was no eosinophilia, and *Filariae* were not seen in spite of a long search.

COMMENT

In spite of the rarity of the condition, a fairly large number of cases of nonparasitic chyluria have been recorded; we have been able to collect over a hundred from the literature. On careful scrutiny, however, some of the cases do not present the cardinal features of true chyluria, and it is obvious that there has been a great deal of confusion between the different forms of milky urine. Chyluria may be simulated by various other substances, such as pus, phosphates or artificial additions, which cause milky opacity of the urine. The most elementary chemical and microscopic examinations of the urine will usually suffice to exclude such errors.

That fat is demonstrated in the urine does not necessarily imply that the fat is due to the presence of chyle. The lipuria which sometimes occurs in diabetes mellitus and rarely in fractures and the pseudo-chyluria of some forms of nephritis must be distinguished from true chyluria. Complete clearing of the opacity when the specimen is shaken with ether and the occurrence of the fat in the form of visible globules usually indicate that the condition is one of lipuria and not of chyluria.

To prove that the milky substance is chyle, it is obviously necessary to show that it possesses most, if not all, of the properties of chyle, i. e., fat-laden lymph. The essential feature of truly chylous urine is the presence of (1) fat, (2) protein and (3) lymphocytes.

Fat.—The fat is usually present in molecular form; that is, the particles are so small that they cannot be seen or separated by centrifugation (Golding-Bird, quoted by Hertz). The molecules of fat are apparently loosely linked with the molecules of protein, because when the fat is dissolved in ether, a precipitate of protein is produced; this

phenomenon has been expressed by most observers as partial clearing after shaking with ether.

Protein.—The protein should be present in the urine, as it is in chyle, in approximately three times the amount of fat. The amount of fat in the chyle is of course variable, depending on the nature of the diet and the state of the digestion. Also, if protein is constantly present in the urine in the intervals between the attacks of chyluria, owing to coincident nephritis, it should be taken into account.

Lymphocytes.—Lymphocytes are present in normal lymph and therefore in chyle. It is curious that previous observers have not specifically noted lymphocytes but have been content to call the cells leukocytes or white corpuscles. Charteris, however, recorded the presence of lymphocytes in his case.

The amount of dextrose in the chyle is only 0.1 per cent, so that the minute quantity which is present in the chylous urine escapes detection by the ordinary copper-reduction tests. Brandenburg described a case of chyluria in a child in whom a fairly high percentage of sugar was present in the urine, but in whom only very transient chyluria existed; this was not proved to be true chyluria.

Blood is normally found in cases of chyluria, presumably coming from the torn superficial blood vessels at the site of the ruptured lymphatic glands. In our case some specimens contained a considerable amount of blood, but the large number of lymphocytes could still be seen.

Having proved that the abnormal constituent in the urine partakes of the character of chyle, one can then separate cases of parasitic origin from the less well defined group of nonparasitic cases, although the mechanism of production is probably similar in both groups. The mere absence of *Filariae* does not negate a past infection, for the parasites may die out and yet obstruct the lymphatic glands by their dead bodies or by secondary inflammatory fibrosis, with the result that, if the patient has been at any time resident in a district in which filariasis is endemic, the chyluria may be assumed to be filarial unless convincing evidence of another etiologic factor is forthcoming.

In the present case, the possibility of filariasis and allied parasitic infestations seemed to be excluded by the fact that, apart from a short holiday in the north of France, the patient had never been outside the British Isles.

Two theories have been advanced as to the mode of production of chyluria. The first of these, now practically abandoned, is called the secretory theory, which supposes that the fat exists in the blood in excess and is passed by the renal epithelium. This theory, however, cannot explain unilateral cases (Kutzmann and Wood), and chemical exami-

nation of the blood has never demonstrated excess of fat, nor have any casts been noted in the urine.

The alternative theory, which was a consequence of the study of parasitic chyluria, may be termed the mechanical theory. That is to say, chyluria is due to the simple admixture of chyle with urine caused by some abnormal communication between the lymphatic vessels and the urinary tract. Such a fistulous condition is preceded by obstruction somewhere between the lymphatic trunks of the mesentery and the upper end of the thoracic duct; back pressure then takes place, the valves become faulty and the lymphatics dilate. Finally, a retrograde flow of chyle takes place via the lumbar channels to the kidney and to the lymphatic vessels of the bladder; these poorly supported vessels give way, and chylous urine is voided. This theory also explains unilateral cases and the presence of blood, which is probably caused by a rupture of the lymphatic varix. The intermittency so frequently noted in chyluria is more readily explicable by this theory than by any other.

Whereas there appears to be little or no doubt that filarial infection may cause lymphatic stasis of such character that chyluria is produced, various other lesions have also been shown to produce it. Because of the rarity and the relatively benign course of nonparasitic chyluria, only a few autopsies have been performed. In some of these, no cause was found for the chyluria (Osler and Roberts). In others, an obstruction of the thoracic duct was demonstrated, but the lymphatic communication with the urinary tract could not be found. Thus, Oehme found secondary malignant glands pressing on the thoracic duct in a case of carcinoma of the stomach with chyluria; in Port's case tuberculous glands compressed the duct at the level of the left bronchus, and Mackenzie demonstrated great dilatation and thickening of the thoracic duct.

Some observers noted dilated lymphatics in relation to the kidney or the bladder but found no cause for the condition (Ponfick, Havelburg and Coryllos and Portocalis). Hertz was able to demonstrate a constriction of the thoracic duct above the diaphragm and a ruptured lymphatic vessel in the wall of the bladder.

The most notable observations were probably those of Pope and Bloch, who in their cases actually saw chyle entering the urinary tract. Such evidence, though not conclusive, goes a long way toward confirming the second, or mechanical, theory of the mode of production of chyluria. In this connection, it must be remembered that the postmortem demonstration of lesions of the lymphatic vessels is a difficult procedure, and unless some special method of injection is used, it is likely that the abnormality will be overlooked.

On reading through the literature on chyluria one is impressed with the fact that all of the cases have shown marked intermittency, the

recurrences of chyluria being in some cases apparently associated with such factors as posture, exercise, diet and pregnancy and in other cases irregular and not obviously related to an extraneous factor. Various theories, some of them rather fantastic, have been put forward to explain the influence of posture, and most of the writers on the subject have been somewhat puzzled by this feature of intermittency.

If one considers the pathologic nature of chyluria, however, the intermittency seems to be natural, for if the generally accepted view is correct, the condition would seem to be analogous to hematemesis occurring in cases of cirrhosis of the liver but affecting the lymphatics instead of the veins. One does not expect continuous hemorrhage from a dilated esophageal varix; when the congestion of the veins is relieved by the bleeding, coagulation and healing tend to follow. Lymph also contains fibrinogen and can form a clot, though the process may be retarded when the site of the rupture is bathed by urine. The freshly formed clot is liable to be broken down when there occurs in the lymphatics a slight increase of pressure such as may be caused by the weight of the column of lymph above the pelvis in the upright posture, if the valves are incompetent, or when muscular action increases the return of the lymph from the lower limbs via the iliac and the lumbar vessels. In the same way, the ingestion of a fatty meal would possibly be sufficient to cause a fresh discharge of chyle by increasing the flow of lymph in the mesenteric vessels.

It is to be noted, too, that the absence of chyle from the urine does not necessarily indicate that the leakage is sealed off, as the lymph in the mesenteric lymphatic glands contains practically no fat in the absence of active absorption of fat from the intestines; it may continue to escape into the urine, giving rise to lymphuria, as was so ably demonstrated by Hertz. Such lymphous urine appears to be quite clear.

In several of the cases of chyluria reported there were long intervals of freedom from the trouble; in the case described here, there was an interval of twelve years during which no chyluria occurred even with the added strain of pregnancy. It is easier to understand such intermissions if chyluria is regarded as an accident in the development of a collateral circulation of lymph in the abdomen.

Anastomotic channels, hitherto quite small, must be dilated in order to convey the lymph by way of the pelvis and the anterior abdominal wall to the right thoracic duct. The modified system can cope well with the flow of lymph, but there are weak points in its course, just as in the esophageal veins in a case of cirrhosis such weak points are often to be found where the vessels can bulge unsupported into a hollow viscus. It does not follow that chyluria will necessarily occur. There must be a relatively large number of cases of partial or complete obstruction of the thoracic duct by aneurysms, enlarged mediastinal glands and growths

in the thorax, as compared with the small number of cases of chyluria. Nor will the discrepancy be accounted for by the occasional occurrence of chylous effusions in the pleural and peritoneal cavities. The immediate cause of the rupture of the weakened lymphatic on the first occasion is usually not obvious, but any subsequent slight rise of tension in the abdominal and pelvic lymphatics may precipitate a fresh escape of lymph, which ceases as soon as the pressure is relieved. Thus repeated attacks of chyluria may occur, until the point of rupture is finally more firmly occluded by the deposition of successive layers of fibrin, and healing takes place.

It seems impossible to advance a convincing explanation of the occurrence of an attack of chyluria just after menstruation; it seemed to occur too often in our case to be merely fortuitous. The onset did not coincide with the stage of premenstrual congestion.

We realize that the report of this case is incomplete; the observations were brought to a sudden end by the cessation of the chyluria during the rest in bed preparatory to cystoscopic examination, and no recurrence has yet taken place. The patient, of course, has never regarded herself as an invalid, and it did not appear justifiable to inconvenience her by too much experimental investigation, especially as the matter is one of chiefly academic interest.

Prof. D. P. Wilkie and Mr. Wade, of Edinburgh, permitted us to use the report of their cystoscopic and pyelographic observations, and our colleague, Dr. Paige Arnold, his roentgenographic report.

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THE ACID-BASE BALANCE IN PATHOLOGIC CONDITIONS

III. SERUM ELECTROLYTE CHANGES IN ACUTE MERCURIC CHLORIDE POISONING

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It has been recognized for a considerable period of time that aside from a marked increase in the nonprotein nitrogen constituents of the blood, a definite lowering of the blood chloride is characteristic of acute mercuric chloride poisoning. In 1915 Woods¹ observed a lowering of the blood chloride in a case of mercuric chloride poisoning. Similar observations have been made by Lewis and Rivers,² Campbell,³ Killian,⁴ Sunderman, Austin and Camack⁵ and Trusler, Fisher and Richardson.⁶ The last mentioned workers also noted marked hypochloremia in dogs given mercuric chloride. Sunderman, Austin and Camack,⁵ in their case of mercuric chloride poisoning, observed in addition to a lowering of chloride a decrease in the serum total base. This has also been the observation of Peters⁷ and Bruckman.

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1. Woods, A. C.: Studies of Nitrogen Partition in the Blood and Spinal Fluid with Especial Reference to the Possible Causation of Albuminuric Retinitis, *Arch. Int. Med.* **16**:577 (Oct.) 1915.

2. Lewis, D. S., and Rivers, T. M.: Chemical Studies on a Case of Bichloride Poisoning, *Bull. Johns Hopkins Hosp.* **27**:193, 1916.

3. Campbell, W. R.: Observations on Acute Mercuric Chloride Nephrosis with a Report of Two Cases, *Arch. Int. Med.* **20**:919 (Dec.) 1917.

4. Killian, J. A.: A Note on the Blood Chlorides in Mercuric Chloride Nephrosis, *J. Lab. & Clin. Med.* **7**:129, 1921.

5. Sunderman, F. W.; Austin, J. H., and Camack, J. G.: Studies of Serum Electrolytes: III. In Infections, Nephritis, and Other Pathological Conditions, *J. Clin. Investigation* **6**:37, 1928.

6. Trusler, H. M.; Fisher, W. S., and Richardson, C. L.: Chemical Changes in the Blood in Mercuric Chloride Poisoning: Mechanism and Significance of Hypochloremia, *Arch. Int. Med.* **41**:234 (Feb.) 1928.

7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 1074.

During the last five years it has been possible to make a study of the acid-base balance of the serum in eleven cases of mercuric chloride poisoning. Since the literature contains relatively few data of this type on a series of cases it seemed desirable to present our observations.

The method of collecting specimens of blood and the procedures employed in studying the acid-base balance were essentially those given elsewhere.⁸

REPORT OF CASES

CASE 1.—F. T., a man, aged 66, was admitted to the hospital on Sept. 16, 1928, twenty-four hours after having taken three tablets of corrosive mercuric chloride. He vomited shortly after taking the drug, and the vomitus contained the greater part of two tablets. Treatment consisted of administering sodium thiosulphate daily, alkaline fluids by mouth and colonic irrigations with alkaline fluids. At no time was the patient anuretic, and he vomited only on the first day of hospitalization. He was discharged from the hospital on September 29.

CASE 2.—H. M., a man, aged 24, was admitted to the hospital on Oct. 8, 1928, about half an hour after having taken three tablets of corrosive mercuric chloride. He vomited shortly thereafter, and the vomitus contained blood. Treatment consisted of the daily administration of sodium thiosulphate, alkaline fluids by mouth and intravenous and subcutaneous injections of dextrose and saline solutions. Anuria developed rapidly, and vomiting and diarrhea persisted. The patient became progressively worse and died on October 17.

CASE 3.—H. S., a woman, aged 36, was admitted to the hospital on May 5, 1929, after having taken five tablets of corrosive mercuric chloride five days previously. Nausea, vomiting and bloody diarrhea had been experienced before admission. Anuria was present at the time of admission. Treatment consisted of daily injections of sodium thiosulphate and daily intravenous injections of 1,500 cc. of dextrose and saline solutions. Vomiting and diarrhea persisted until death on May 12.

CASE 4.—S. T., a woman, aged 25, was admitted to the hospital on May 12, 1929, shortly after having taken seven tablets of corrosive mercuric chloride dissolved in hot water. Vomiting occurred a short time thereafter and continued throughout the illness. Anuria developed rapidly and persisted. The treatment consisted of daily injections of sodium thiosulphate and the administration of colonic irrigations and alkaline fluids by mouth. The patient died on May 17.

CASE 5.—P. H., a man, aged 44, was admitted to the hospital on March 7, 1930, an hour and a half after having taken sixteen tablets of corrosive mercuric chloride. Almost immediately thereafter the patient vomited. Milk and white of egg were given. When he was brought to the hospital gastric lavage yielded a large amount of bloody material. Anuria developed rapidly. There were considerable vomiting and diarrhea. The treatment consisted of daily injections of sodium thiosulphate, Fischer's solution (sodium chloride, 1.4 per cent, and sodium carbonate, 2 per cent) administered intravenously and colonic irrigations. The patient became progressively worse and died on March 12.

8. Muntwyler, E.; Way, C. T., and Binns, D.: The Acid-Base Equilibrium in Pathological Conditions: II. Alkalosis Observed in Hypertensive States, *J. Clin. Investigation* 10:489, 1931.

CASE 6.—M. C., a woman, aged 35, was admitted to the hospital on April 3, 1930, shortly after having taken six tablets of corrosive mercuric chloride dissolved in water. When brought to the hospital she was given gastric lavage. Vomiting persisted for several days. The patient was never completely anuretic. The treatment consisted of daily injections of sodium thiosulphate, the administration of alkaline fluids by mouth and alkaline colonic irrigations. The patient improved rapidly and was discharged from the hospital on April 19.

CASE 7.—C. B., a woman, aged 26, was admitted to the hospital on April 18, 1933, two days after having taken five tablets of corrosive mercuric chloride. The patient vomited almost immediately and continued to vomit throughout the period of hospitalization. Egg albumin was given. Anuria developed rapidly and remained practically complete until death on April 24. The treatment consisted of gastric lavage, daily injections of sodium thiosulphate, intravenous injections of saline and dextrose solutions and the administration of fluids by mouth.

CASE 8.—E. B., a woman, aged 24, was admitted to the hospital on April 17, 1933, after having taken two tablets of corrosive mercuric chloride. Milk was given shortly thereafter, and vomiting occurred. The vomitus showed fragments of the tablets. The history revealed that the patient had employed two tablets of corrosive mercuric chloride dissolved in a quart (946 cc.) of water for a vaginal douche for a considerable period of time; this practice, however, was discontinued when irritation, vaginal pain and nocturia were noted, several months before admission. When admitted she was given gastric lavage. The treatment consisted of daily injections of sodium thiosulphate, colonic irrigations and large intravenous and subcutaneous injections of saline solution. The patient was essentially anuretic for six days and then began to excrete small amounts of urine. As urinary excretion increased the nonprotein nitrogen constituents of the blood decreased and the patient rapidly improved. She was discharged from the hospital on May 20. In the early days of hospitalization there were considerable vomiting and diarrhea.

CASE 9.—M. K., a woman, aged 22, was admitted to the hospital on May 26, 1933, shortly after having taken six tablets of corrosive mercuric chloride on an empty stomach. Vomiting occurred almost at once. When brought to the hospital she was given gastric lavage. After the first day of hospitalization anuria developed and continued until death on June 6. The treatment consisted of daily injections of sodium thiosulphate, large subcutaneous and intravenous injections of saline solution and colonic irrigations.

CASE 10.—L. M., a woman, aged 19, was admitted to the hospital on June 3, 1933, thirty minutes after having taken three tablets of corrosive mercuric chloride. Vomiting occurred before admission. When she was admitted to the hospital gastric lavage was given. Severe vomiting persisted, and the patient rapidly became anuretic. The treatment consisted of daily injections of sodium thiosulphate, large intravenous and subcutaneous injections of saline solution and colonic irrigations. The patient rapidly became worse and died on June 7.

CASE 11.—J. T., a man, aged 41, was admitted to the hospital on June 19, 1933, about thirty minutes after having taken five tablets of corrosive mercuric chloride. He vomited several times prior to admission. When he was brought to the hospital gastric lavage was given, and 15 grains (1 Gm.) of sodium thiosulphate was administered intravenously. Milk and saline solution were given by mouth. On June 21, an infusion of saline and dextrose solution (4,000 cc.) was given, and on June 22, an infusion of Ringer's solution (2,000 cc.). The latter was given daily until death on June 25. During the first day of hospitalization 75 cc. of

urine was excreted. From the second day until death the patient was practically anuretic. Severe vomiting was present during the first four days. Bloody diarrhea persisted throughout.

OBSERVATIONS

In the table are given the changes in the acid-base balance of the serum in eleven cases of acute mercuric chloride poisoning. It is readily

Changes in the Serum Acid-Base Balance in Acute Poisoning by Mercuric Chloride

Case	Date	p _H	Serum					Blood			Comment	
			Bicarbonate, M.Eq.	Chloride, M.Eq.	Protein, M.Eq.	Total Determined Acid, M.Eq.	Total Base, M.Eq.	Undetermined Acid, M.Eq.	Urea Nitrogen, Mg. per 100 Ce.	Nonprotein Nitro- gen, Mg. per 100 Ce.		Creatinine, Mg. per 100 Ce.
1	9/17/28	37	82	2.7	Drug* taken 9/15/28	
	9/18/28	7.45	23.84	86.9	134.1	
	9/24/28	21	40	1.9	Discharged 9/29/28	
2	10/ 9/28	71	4.1	Drug taken 10/8/28	
	10/10/28	5.8	
	10/16/28	7.31	14.76	84.8	17.7	117.26	131.5	14.2	Died 10/17/28
3	5/ 7/29	113	..	20.0	Drug taken 5/1/29	
	5/10/29	7.26	18.36	45.6	119.0	Died 5/12/29	
4	5/15/29	7.27	15.30	82.8	15.3	113.40	133.0	19.6	Drug taken 5/12/29
	5/16/29	7.22	14.40	82.1	134.1	Died 5/17/29
5	3/10/30	102	..	10.0	Drug taken 3/7/30	
	3/12/30	7.07	7.03	81.8	15.7	104.53	141.6	37.1	105	..	19.5	Died 3/12/30
6	4/ 8/30	180	12.0	Drug taken 4/3/30	
	4/ 9/30	7.42	17.26	77.5	18.7	113.46	130.8	17.3
	4/16/30	7.41	19.10	75.5	134.8	Discharged 4/19/30
7	4/21/33	113	14.2	Drug taken 4/16/33	
	4/24/33	7.34	19.60	66.5	14.9	101.00	149.0	48.0	169	12.2	Died 4/24/33
8	4/18/33	4.6	Drug taken 4/17/33	
	4/24/33	7.14	12.25	72.2	16.0	100.45	143.0	42.5	204	15.3
	4/28/33	7.24	18.45	80.2	14.1	112.75	150.6	37.8	193	15.5
	5/ 4/33	7.39	28.30	83.1	20.7	132.10	148.1	16.0	142	10.6
	5/13/33	7.48	28.70	98.2	19.8	146.70	148.4	1.7	34	3.3	Discharged 5/20/33
	5/24/33	7.38	24.35	103.0	20.3	147.65	147.2	32	1.6
9	5/27/33	7.41	23.00	84.6	16.5	124.10	147.5	23.4	79	6.6	Drug taken 5/26/33
	6/ 5/33	7.32	14.08	77.6	12.1	103.78	138.7	34.9	57	..	9.4	Died 6/6/33
10	6/ 5/33	7.36	18.46	90.6	16.1	125.16	152.1	26.9	37	..	5.1	Drug taken 6/3/33
	6/ 7/33	7.14	11.26	92.2	12.7	116.16	149.0	32.8	..	108	4.6	Died 6/7/33
11	6/21/33	7.39	19.70	94.6	13.7	128.00	143.3	15.3	39	6.2	Drug taken 6/19/33
	6/24/33	7.21	14.60	91.6	13.1	119.30	148.1	28.8	86	11.3	Died 6/25/33

* Corrosive mercuric chloride.

apparent that in most instances there was a marked tendency to an uncompensated acidosis accompanied by a lowering of both the serum chloride and the serum total base. The lowest p_H and bicarbonate content were encountered in case 5, in which a p_H of 7.07 and a bicarbonate content of 7.03 milliequivalents were observed. The lowest chloride and total base were observed in case 3, namely, 45.6 and 119 milliequivalents, respectively. With the lowering of the concentration of bicarbonate and chloride the undetermined acid fraction (representing phosphate, sulphate and organic acid) tended to be increased. The

highest value for the undetermined acid (48 milliequivalents) was observed in case 7. The initial specimen from case 8 showed an undetermined acid value of 42.5 milliequivalents. With recovery and coincident elevation of the bicarbonate and chloride concentrations, the undetermined acid decreased to a small value.

COMMENT

The characteristic loss of chloride and total base from the blood in cases of acute mercuric chloride poisoning is undoubtedly due chiefly to a loss resulting from the accompanying vomiting and diarrhea. That vomiting is probably a factor in the loss of chloride was recognized by Lewis and Rivers.² They observed that the blood chloride decreased regularly during the period of vomiting and rose after the vomiting had stopped. Trusler, Fisher and Richardson,⁶ using dogs, concluded that vomiting was the most important factor. They found that rabbits, which do not vomit, when poisoned with mercuric chloride did not show a marked reduction of the blood chloride. The latter workers also observed a case of mercuric chloride poisoning and found that the decrease in chloride was too great to be accounted for by loss as a result of vomiting. In this case they believed that the loss was brought about by colonic irrigations and gastric lavage, and pointed out that such routine treatment might cause excessive loss of chloride. This danger, they added, can no doubt be mitigated by including physiologic solution of sodium chloride as a component of such solutions.

With loss of fluid from the intestinal tract in cases of mercuric chloride poisoning the patient becomes markedly dehydrated, which results in anuria. The value of forcing fluid in the treatment of mercuric chloride poisoning was brought out experimentally by Haskell, Carder and Coffindaffer⁹ in their experiments with dogs. A large percentage of their dogs survived what was considered a fatal dose when given intravenous injections of salt solutions comparatively soon after the oral administration of the poison. Hayman and Priestly¹⁰ emphasized that the maintenance of adequate diuresis during the period of diminished concentration ability forms an essential part of the treatment of mercurial nephrosis. Killian⁴ reported the recovery of two patients who, in addition to other treatment, received 0.7 per cent sodium chloride by hypodermoclysis. Consequently, as pointed out by Peters and Van Slyke,⁷ it seems that the most important therapeutic measure

9. Haskell, C. C.; Carder, J. R., and Coffindaffer, R. S.: The Value of Forcing Fluid in the Treatment of Mercuric Chloride Poisoning, *J. A. M. A.* **81**:448 (Aug. 11) 1923.

10. Hayman, J. M., Jr., and Priestly, J. T.: The Importance of Diuresis in the Treatment of Certain Cases of Mercuric Chloride Poisoning, *Am. J. M. Sc.* **176**:510, 1928.

is an early administration of saline solution intravenously or subcutaneously. This tends to restore to normal the fluid and salt content of the body and to prevent anuria. It is necessary to begin the administration as quickly as possible, for when anuria occurs the recovery of the patient is questionable. Some patients who are not completely anuretic die quickly even though large amounts of saline solution have been administered. In these persons death may undoubtedly be attributed in a large part to shock.¹¹ That shock was a considerable factor in the rapidly fatal outcome in cases 9 and 10 is unquestionable. These persons were given large intravenous and subcutaneous injections of saline solution immediately, but they remained toxic throughout and soon died.

Of the eleven cases reported recovery occurred in three. Of these three, case 8 is of interest. In this case there was prompt and persistent administration of saline solution. The initial specimen of blood, obtained seven days after the patient had taken the poison, showed a marked uncompensated acidosis and a lowered chloride concentration. Complete anuria was present. During the following month of observation and treatment the bicarbonate and chloride concentrations rose to their normal levels. In this return to normal the bicarbonate concentration rose more rapidly to a maximum than did the chloride and then fell slightly with the further increase in chloride. The constituents of non-protein nitrogen mounted rapidly during the period of anuria. When, however, excretion of urine was resumed, these constituents quickly returned to normal.

SUMMARY

A study of the acid-base balance of the serum was made in eleven cases of acute mercuric chloride poisoning. The chief disturbances were an uncompensated acidosis, lowering of the chloride and total base and an elevation of the undetermined acid (representing phosphate, sulphate and organic acid).

The therapeutic measures are briefly presented, with emphasis on early intravenous or subcutaneous administration of saline solution to restore to normal the fluid and salt content of the body and to prevent anuria.

11. MacNider, W. deB.: A Study of Acute Mercuric Chloride Poisoning Intoxication in the Dog with Special Reference to Kidney Injury, *J. Exper. Med.* **27**:519, 1918.

CONGESTIVE HEART FAILURE

XX. CHEYNE-STOKES RESPIRATION AS THE CAUSE OF PAROXYSMAL DYSPNEA AT THE ONSET OF SLEEP

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The starting point of our observations was the fact, noted in a previous study,¹ that patients who complained of seizures of dyspnea at the onset of sleep frequently were observed to have periodic breathing. This was in accord with the statement of Sir James Mackenzie,² who wrote:

Another form of distressed breathing is Cheyne-Stokes respiration. Many elderly people exhibit Cheyne-Stokes respiration without being conscious of it. But in certain forms of heart failure it may occur and becomes so marked that the patient's rest is disturbed during the period of increased breathing. This is preceded by a period when the breathing almost ceases or completely ceases; it may be for a period of half a minute to a minute during which the patient may fall asleep to be awakened up, it may be by a sense of suffocation; on its resumption the breathing is often exaggerated. . . . Occasionally the periods of apnea are so complete and prolonged that the patient wakes up with a sense of great distress, sometimes so severe that he may spring out of bed in his extremity and may then have to breathe heavily and in laboured fashion for many minutes. This is the condition which has received the term "cardiac asthma."

This observation led us to study a group of patients with hypertensive, arteriosclerotic and syphilitic heart disease who had repeated attacks of congestive heart failure over a period of many months. To measure the ventilation was not found feasible as the procedures involved prevented sleep. Consequently it was decided to employ the simple expedient of recording the respirations by means of a pneumograph, a writing pen and a kymograph of the type used with the Benedict-Roth

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1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, *Arch. Int. Med.* **53**:561 (April) 1934.

2. Mackenzie, James: *Diseases of the Heart*, ed. 4, New York, Oxford University Press, 1925, p. 33.

metabolism apparatus. The records of respiration were usually made in the evening between the hours of 8 and 11. As a rule, the patients readily fell asleep when noise was prevented and the lights were turned off, a flash-light being used to watch the tracings on the kymograph. In some instances it was necessary to resort to sedatives, but these were avoided whenever the patient could sleep without them.

In order to clarify the relationship of periodic breathing to dyspnea occurring at the onset of sleep we have attempted to answer the following questions: 1. How frequently do persons who complain of respiratory distress during sleep exhibit Cheyne-Stokes breathing? 2. Why does periodic breathing so frequently occur during sleep? 3. What relation exists between the objective respiratory alterations and the subjective feeling of distress? 3. What is the rôle of the blood gases in producing these objective and subjective phenomena? It may be stated at this point that our observations have shown that two factors are of especial importance in relation to periodic breathing and dyspnea appearing at the onset of sleep. These are (*a*) overventilation and (*b*) depression of the respiratory center occurring suddenly when the subject passes from the waking to the sleeping state. We shall now consider the results of observations in detail.

OBSERVATIONS

1. *Frequency of Cheyne-Stokes Respiration in Patients Complaining of Paroxysmal Dyspnea Occurring at the Onset of Sleep.*—If Mackenzie's theory of the mechanism of paroxysmal dyspnea is correct, one should be able to demonstrate that every patient with this syndrome also has Cheyne-Stokes respiration. For several months we observed hospitalized patients with paroxysmal dyspnea in order to determine whether or not this is the case. It was soon found that many patients of this type do not have Cheyne-Stokes respiration. The patients without periodic breathing usually had their paroxysms of dyspnea after sleeping for one or more hours; none of them had attacks coming on at the onset of sleep. On the other hand, every patient who complained of dyspnea as sleep came on had periodic breathing. During the day the breathing may be regular, but rhythmic variations develop as the patient goes to sleep. In one instance we were unable to observe periodic breathing by inspection, but respiratory curves showed that it was present. Probably there are exceptional cases, but up to the present time we have found none, and it seems safe to state that, as a general rule, patients with attacks of dyspnea coming at the onset of sleep exhibit Cheyne-Stokes respiration. Furthermore, as clinical improvement sets in the cycles gradually diminish in intensity, and simultaneously the paroxysms of dyspnea become less frequent and less severe. Finally

they disappear, but the breathing remains periodic for a longer time and then becomes regular. The important point is that the attacks subside entirely before the periodicity disappears completely. In chart 1 are shown respiratory curves of two patients, both of whom had severe paroxysmal dyspnea coming at the onset of sleep at the time the first (upper) tracings were made and milder dyspnea during the day with each hyperpneic phase of the cyclic breathing. The second records (B) were taken in both cases after there had been marked clinical improvement and when the patients were still having occasional mild respiratory distress on going to sleep but none during the day. The later curves

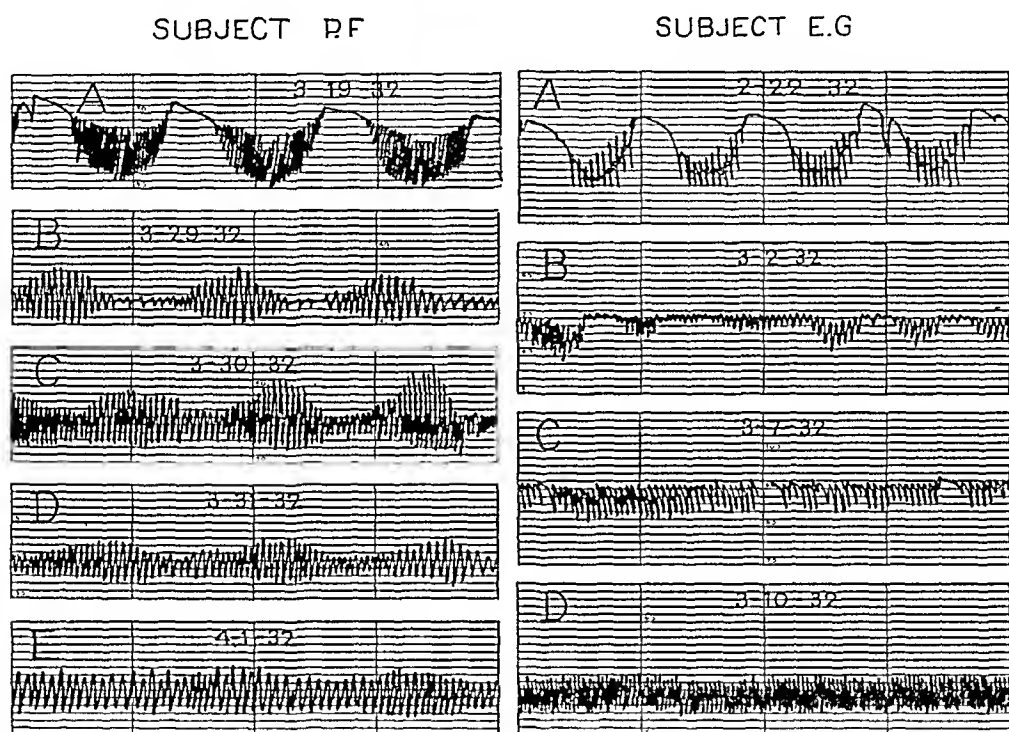


Chart 1.—The curve passes from right to left. The distance between two adjacent vertical lines represents one minute. The successive curves illustrate the progressive gradual disappearance in both patients of Cheyne-Stokes respiration as clinical improvement occurred. When the first tracings (A) were taken both patients had severe paroxysmal dyspnea, diurnal as well as nocturnal. At the time of the second tracings (B) they had mild attacks on going to sleep but none during the day. When the later records were made both patients were free from subjective respiratory distress.

(C, D, E) were all taken after the patients were free from dyspneic seizures. It can be seen that periodic breathing persisted in a mild form for a few days after the cessation of paroxysms, but finally the breathing became regular.

2. *Effect of Sleep on the Respiratory Curve.*—To determine whether the breathing of patients of the type under discussion underwent further alteration during the transition from the waking to the sleeping state,

the time at which subjective respiratory distress is most marked, tracings were made in the evening before, during and after the onset of sleep.

In all instances an attempt was made to estimate the exact status as regards sleep. As used throughout this paper and on the curves the term "awake" implies full consciousness; "dozing" means a somnolent state in which the patients when roused answered spoken questions but did not respond to whispers; "light sleep" signifies that the patient was definitely asleep and could be roused only with some difficulty. The unqualified term "sleep" is used to designate the instances in which the patient was definitely not awake but in which we were unable to decide just how deeply asleep he was.

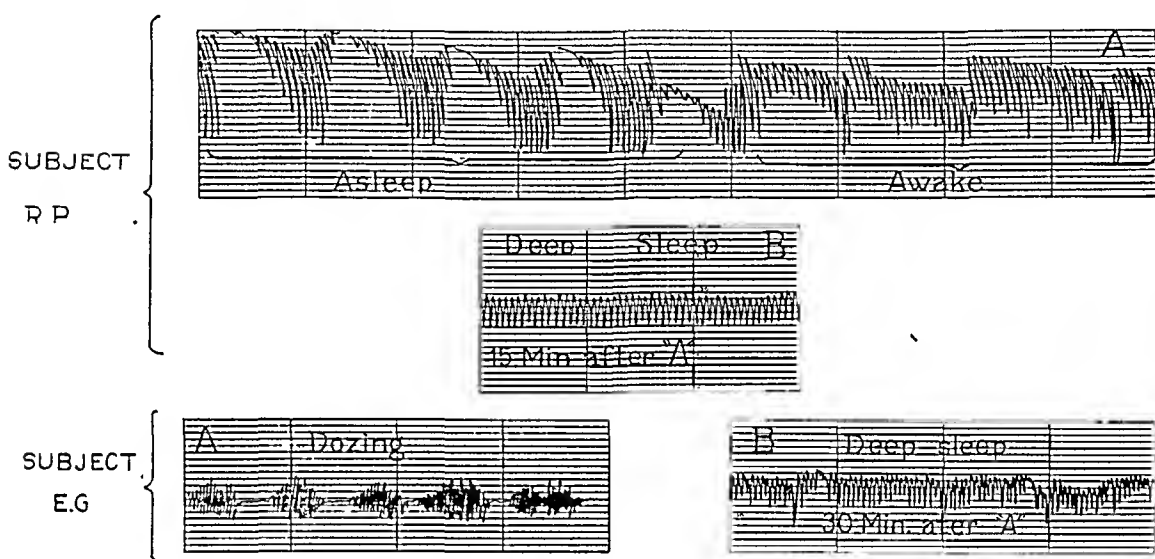


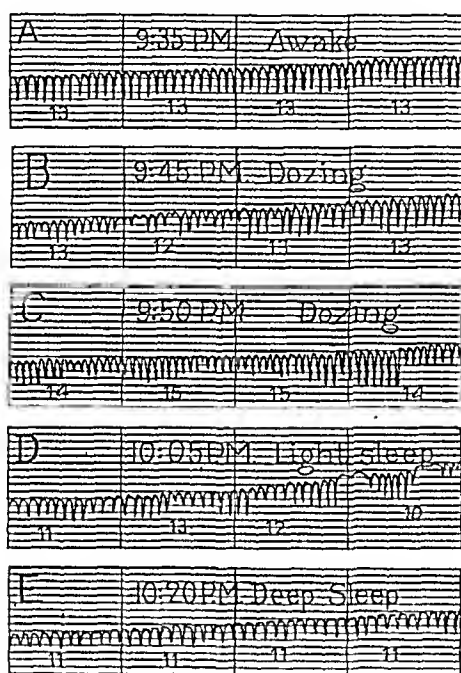
Chart 2.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. During the somnolent state both subjects showed well marked Cheyne-Stokes respiration which tended to disappear in deep sleep.

In a number of instances the patients went to sleep rather abruptly, and we could be certain to within a few seconds as to the exact time of the onset of sleep. Examples are shown in chart 2 (subject R. P., curve A) and in chart 3 (subject E. G., curves A, B, C and D). While awake some of the subjects had periodic breathing and some did not. At the moment sleep began, the breathing became less pronounced. Sometimes there was total apnea, and sometimes only a marked decrease in the depth of breathing. Following this initial apnea (relative or absolute) there occurred a period of hyperpnea. (Throughout this paper the term "dyspnea" is used to mean subjective respiratory discomfort, while "hyperpnea" designates the phase of heightened respiratory activity.) This hyperpnea usually lasted about one-half minute and was

followed by a second phase of depression, often more marked than the first, which in turn was likely to be followed by a second hyperpneic phase, and so on, the result being Cheyne-Stokes respiration. In many cases this set in at the moment of sleep; in others it was already present but increased in severity.

In other instances (chart 3, subject J. W. C.) the transition from the waking to the sleeping state was much more gradual. Then the respiration gradually became periodic as the patient dozed. During light sleep the cycle would become more pronounced and there would be occasional short periods of apnea, followed by hyperpnea. During the latter phases the ventilation usually seemed to be greater than during

SUBJECT J.W.C.



SUBJECT E.G.

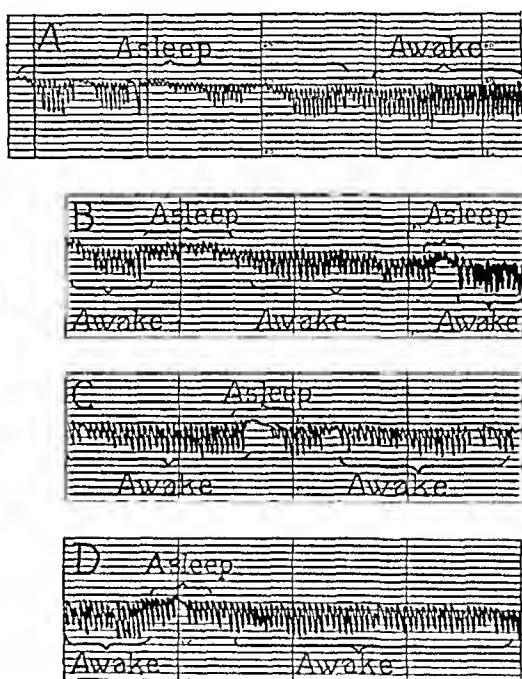


Chart 3.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. At the onset of sleep respiratory depression developed, and this was followed by periodic breathing (E.G.). Awakening was associated with greater breathing. The changes in the other subject (J.W.G.) were more gradual but similar. While he was awake the respiration was regular. When he became sleepy and began to doze, periodic breathing developed and after a time there was actual apnea. With the onset of deep sleep the respiration again became regular.

the previous waking period when the breathing was regular. This was judged from the curves, which, being pneumographic and not spirometric tracings, gave accurate information as regards the respiratory rate but may have been misleading in respect to tidal air.

In still other instances there was rapid alternation in the level of consciousness, the subject dozing during hyperpnea and sinking into definite sleep at the onset of apnea. This phenomenon is well recognized

as frequently occurring in patients with Cheyne-Stokes respiration in various diseases. An example of this type of record is seen in chart 2 (subject E. G., curve *A*).

One important feature which was almost invariably observed was the tendency of periodic breathing to disappear entirely or to become much less marked as the subject sank into deep sleep (charts 2 and 3). The only exceptions to this general rule occurred in some of the instances in which morphine had to be administered in large doses in order to induce sleep. Even under such conditions the periodic breathing usually became less pronounced or disappeared as deep sleep developed, but in some cases the reverse effect occurred, the periodicity becoming progressively more pronounced as sleep became more profound. This exceptional result seems to have been related to the action of the drug and does not invalidate the general rule that Cheyne-Stokes breathing becomes more pronounced at the onset of sleep and then tends to disappear, provided, of course, that the subject remains asleep.

Somewhat similar results have been found in normal subjects by Reed and Kleitmann.³ They noted that the respiration often became irregular during somnolence, and in some instances definite Cheyne-Stokes breathing occurred. As the subjects sank into sound sleep the respiration again became regular.

3. Subjective Distress in Breathing in Relation to the Respiratory Curve.—When tracings were being taken on persons who were subject to attacks of paroxysmal dyspnea the patient was instructed to tell us whenever he felt short of breath. In chart 4 are shown examples of the respiratory curves obtained at such times. In the upper left record (*A*) four cycles of Cheyne-Stokes breathing are shown, and it can be seen that the hyperpneic phase was more marked in two of these cycles than in the other two. The onset of dyspnea coincided with the development of marked hyperpnea, as would be expected. In many instances these phases of unusually severe hyperpnea occurred following several cycles during which the apnea became progressively longer as the patient sank into sleep. Then following a long period of apnea the subject would awake as breathing set in. On awakening, the hyperpneic phase would be considerably more marked than in the previous cycles when the patient was asleep or dozing, and coincidentally dyspnea would be severe until the next apneic phase occurred. This sequence of events is illustrated in curves *B* and *D* of chart 4.

In some instances the awakening was immediately preceded by coughing, and the cough seemed to be the "trigger" which caused the patient to awake (chart 4, curve *C*). More commonly cough occurred after the patient had awakened and either during the crescendo part

3. Reed, C. I., and Kleitmann, N.: *Am. J. Physiol.* **75**:600, 1926.

of hyperpnea or at its height. Whenever the patient awakened, the hyperpneic phase became temporarily more pronounced than during the preceding cycles when the patient had been asleep. This phenomenon is of fundamental importance to a proper understanding of the mechanism of the dyspnea and will be discussed later.

Frequently records of the type illustrated by curve *E* in chart 4 were obtained. In these cases the patient slept during each apneic phase and usually awoke with dyspnea during the crescendo portion of the

SUBJECT E G

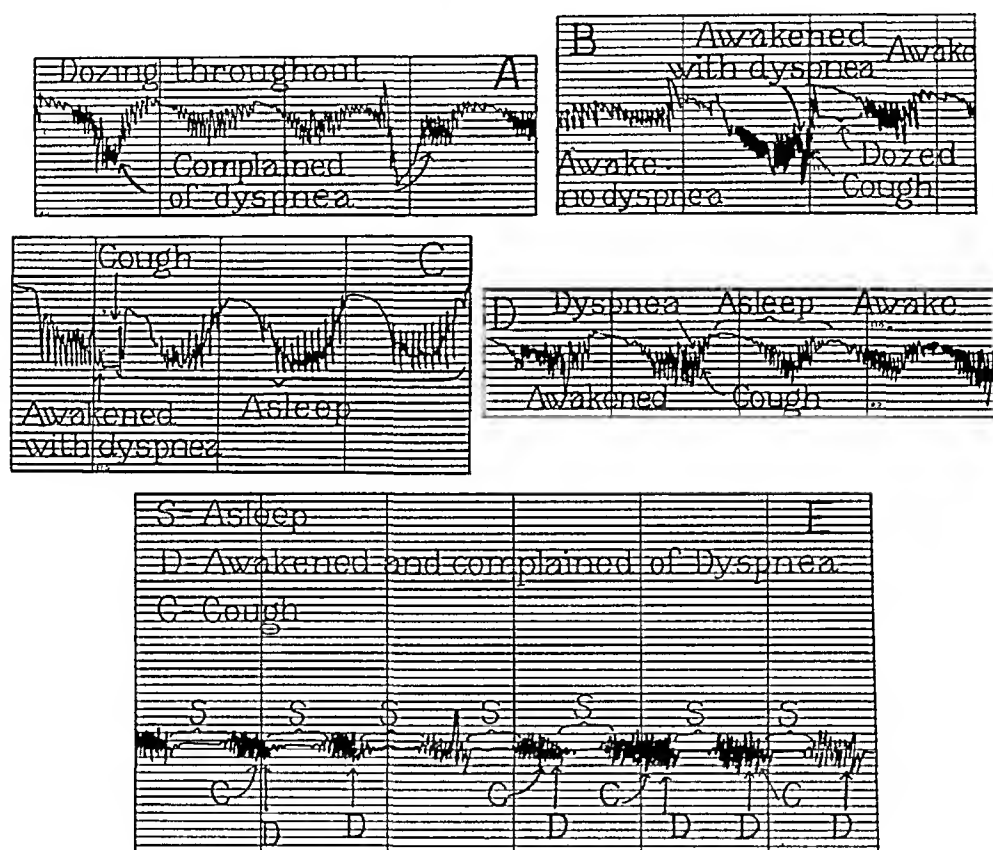


Chart 4.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. During the apneic periods the patients tended to doze. Awakening and subjective distress occurred during the crescendo portion of the hyperpneic phase and was associated with an increase in the degree of hyperpnea as compared with the same phase when asleep (*A*, *B* and *C*). On the patient's sinking into sleep there was a tendency for each apneic cycle to become longer until he awakened with subjective dyspnea at the end of an unusually long period of apnea (*D*). Coughing sometimes occurred just before the awakening and at the onset of hyperpnea (*C*); in other instances the cough came after awakening and at the height of hyperpnea (*E*). In the lower curve (*E*) the patient slept during each apneic phase and awakened each time hyperpnea set in.

hyperpneic phase. Occasionally he would remain asleep during hyperpnea, and the record usually showed that this particular cycle was characterized by less violent hyperpnea than the other ones in which he awakened.

With patients who have extremely severe dyspnea one may sometimes obtain curves similar to *D* in chart 4 throughout the whole twenty-four hour period. Such patients are exhausted and fall asleep toward the end of each hyperpneic period. The sleep lasts for from a few seconds to a minute, and then shortly after the resumption of breathing the subject wakes; the breathing becomes still more labored for perhaps a minute or less, and the cycle then repeats itself. Such patients may live for days and never sleep more than a few minutes or seconds at

SUBJECT E.G.

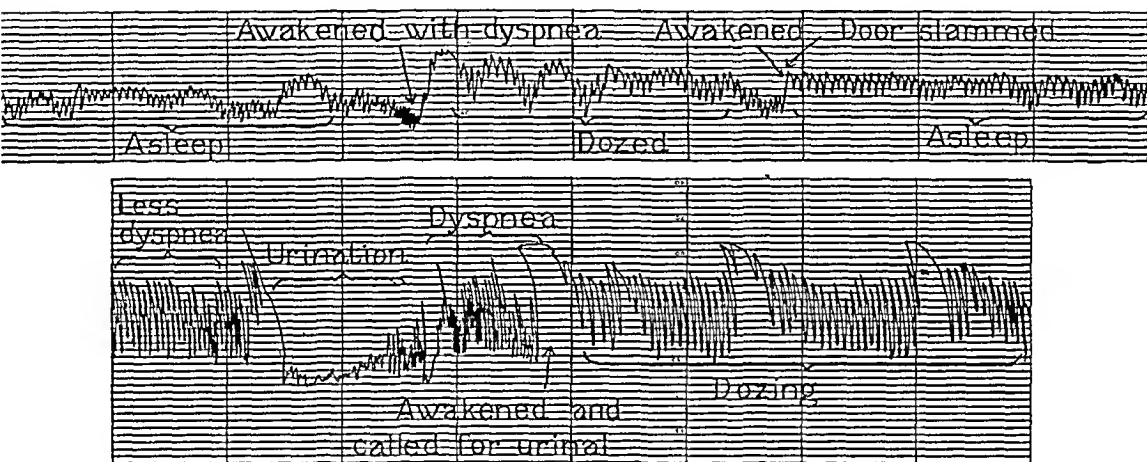


Chart 5.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. At the beginning of curve *A* the subject was asleep. When a door slammed he did not immediately awaken but did show an increase in breathing which was followed by several cycles of respiratory periodicity. At length apnea developed, and following this he suddenly awakened with marked hyperpnea and subjective distress. In curve *B* is illustrated the awakening caused by the desire to urinate and associated with hyperpnea and dyspnea. During urination there was respiratory inhibition and then, the patient being awake, the breathing remained greater than when he had been sleeping but not as marked as just before urination.

a time unless they receive sedatives. With improvement in their clinical state the cycles become less marked. With the onset of sleep the apneic phases become progressively longer and the hyperpneic periods more marked until the patient awakes with a dyspneic paroxysm which is simply an unusually severe hyperpneic phase. If, however, this barrier is once passed and sound sleep comes on, the breathing becomes relatively regular and remains so as long as the deep sleep persists.

4. *Effect of Various Stimuli on the Respiratory Curve.*—Any factor which either causes the patient to awaken or decreases the depth of sleep tends to precipitate Cheyne-Stokes respiration and thereby to cause attacks of paroxysmal dyspnea. Cough is probably the most frequent and important of such factors (chart 4) but a number of others have been noted, and examples are shown in charts 5 and 6. The slamming of a door in an adjacent corridor (chart 5, curve *A*) caused the respiration, which had been only slightly irregular, to increase and then become periodic. After several cycles of rhythmic breathing, apnea occurred.

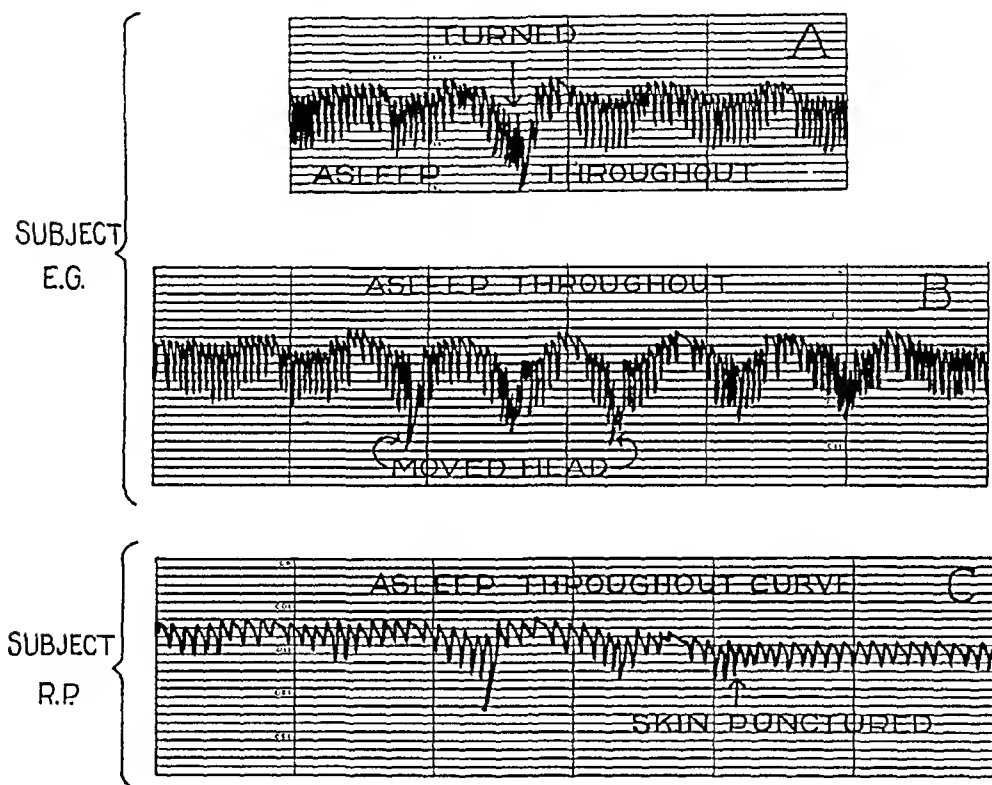


Chart 6.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. Movements of the body were associated with respiratory augmentation and a corresponding increase in the degree of periodicity. A more striking effect was obtained by puncturing the skin. Although the patient remained asleep the stimulus was followed by periodic breathing which was progressive for several cycles and then gradually disappeared. It seems evident that the increased breathing produced by the stimulus was responsible for the subsequent periodicity.

With the onset of the next hyperpneic phase the subject awakened and complained of dyspnea, and at this time there was marked augmentation of the breathing. This was followed by a phase of depression, and the subject then gradually returned to sleep.

A similar cycle of events was observed in the same patient on several other occasions, the precipitating factor in these instances being the desire for urination. An example is shown in curve *B* of chart 5.

While half asleep the patient suddenly awoke and called for the urinal. Until this was brought to him he remained extremely dyspneic. As soon as he began to urinate his dyspnea disappeared, and a phase of diminished breathing set in. As stated, this series of events was observed on several occasions, and the patient volunteered the information that many of his dyspneic seizures were precipitated by the desire for urination.

The effect of such "trigger" factors is most marked when they cause the patient to awaken, but definite changes in the respiratory curve can be observed as a result of stimuli which are not sufficiently strong to cause awakening. Examples are shown in chart 6. Turning the body (*A*) or moving the head (*B*) caused well marked increase in the degree of the periodicity of the breathing, which had previously been only slightly irregular. The effect of sticking the skin with a needle (*C*) was even more pronounced; periodic breathing developed, becoming progressively more marked for three cycles and then gradually disappearing.

As a result of the tracings exemplified by charts 4, 5 and 6 one may summarize the relation of stimuli to paroxysmal dyspnea of the type under consideration as follows: Many types of bodily stimuli tend to cause an immediate increase in respiration which is likely to be followed by periodic breathing even though the patient remains asleep. If the stimulus is strong enough to awaken the patient, the hyperpnea is more marked and is likely to be associated with subjective dyspnea. Following this severe hyperpnea periodic breathing usually becomes exaggerated for a few cycles, and there may be subjective distress with each hyperpneic phase of these cycles.

5. Production of Periodic Breathing by Overventilation.—The observations which have just been cited suggest that the immediate cause of onset of Cheyne-Stokes respiration occurring in response to a stimulus is overventilation. That this assumption is probably correct is indicated by chart 7 in which it is shown that periodic breathing could be produced by voluntary hyperpnea both in normal subjects and in a patient with cardiac disease. This observation is in no sense original since it was shown by Douglas and Haldane⁴ in 1909 that forced breathing in man could cause periodic breathing, and their observation was confirmed by King,⁵ who produced typical Cheyne-Stokes respiration in dogs by the same means.

It is planned to publish at a later date the results of a clinical and experimental study of the mechanism of Cheyne-Stokes respiration in general, and at that time the results of our observations in regard to

4. Douglas, G. C., and Haldane, J. B.: *J. Physiol.* **38**:401, 1909.

5. King, C. E.: Unpublished observations.

the blood gases of patients with cardiac and other diseases will be presented in detail. At present we prefer to draw no conclusions concerning the mechanism of Cheyne-Stokes respiration in general, but it may be stated that in regard to the periodic breathing occurring in patients with cardiac failure there appear to be at least two important physiologic factors, which are:

(a) Overventilation Due to Reflex Stimulation of Breathing: In other studies of the present series it has been shown that congestion of the lungs⁶ and a rise in venous pressure⁷ produce reflex increase in

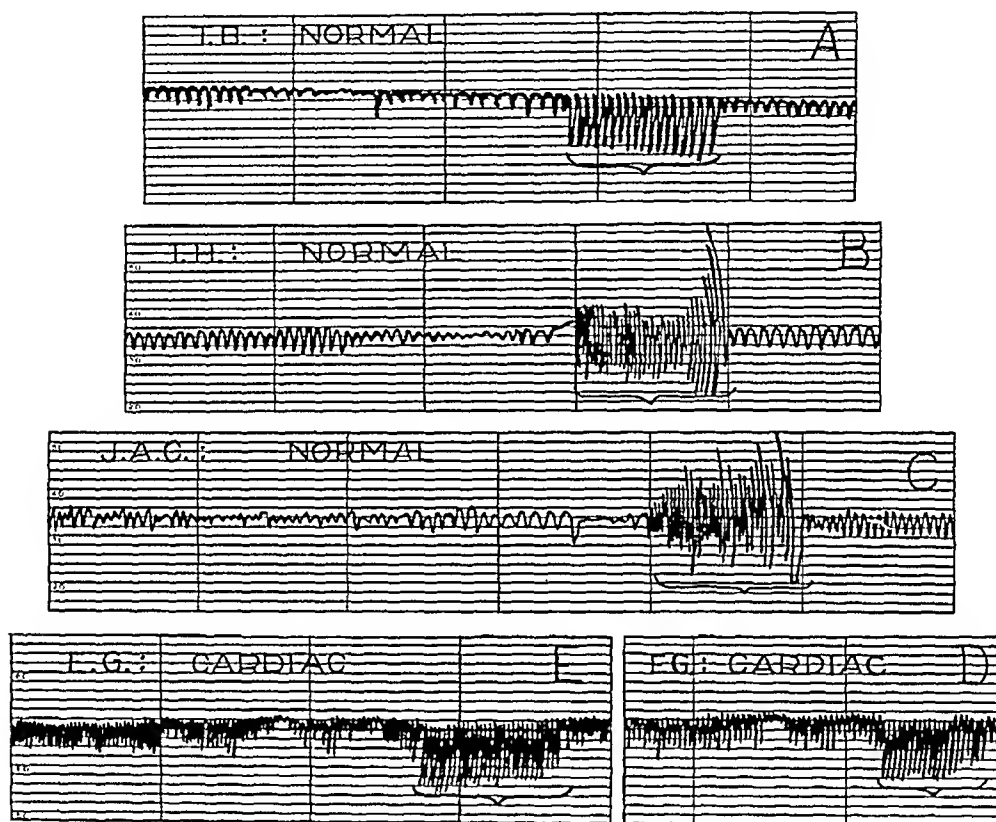


Chart 7.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. Voluntary overventilation was followed by respiratory depression in all subjects, and during the recovery from this the breathing was periodic.

breathing. This leads to excretion of carbon dioxide and eventually, when the respiratory depression due to the loss of the gas becomes sufficiently marked to overbalance the reflex stimulation of breathing, apnea results. At the end of apnea there is both chemical and reflex stimulation of breathing, and another cycle results. That this sequence

6. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: *J. Clin. Investigation* **11**:133, 1932; Harrison, T. R.; Harrison, W. G., and Marsh, J. A.: *Am. J. Physiol.*, to be published.

7. Harrison, T. R.; Harrison, W. G., and Marsh, J. A.: *Am. J. Physiol.* **100**:417, 1932.

of events plays a rôle in the production of Cheyne-Stokes respiration is indicated by the fact that the majority of patients with cardiac failure and Cheyne-Stokes respiration do have abnormally low values for arterial carbon dioxide tension. However, overventilation cannot be regarded as the sole factor because some patients with cardiac failure and Cheyne-Stokes respiration have had normal values for arterial carbon dioxide

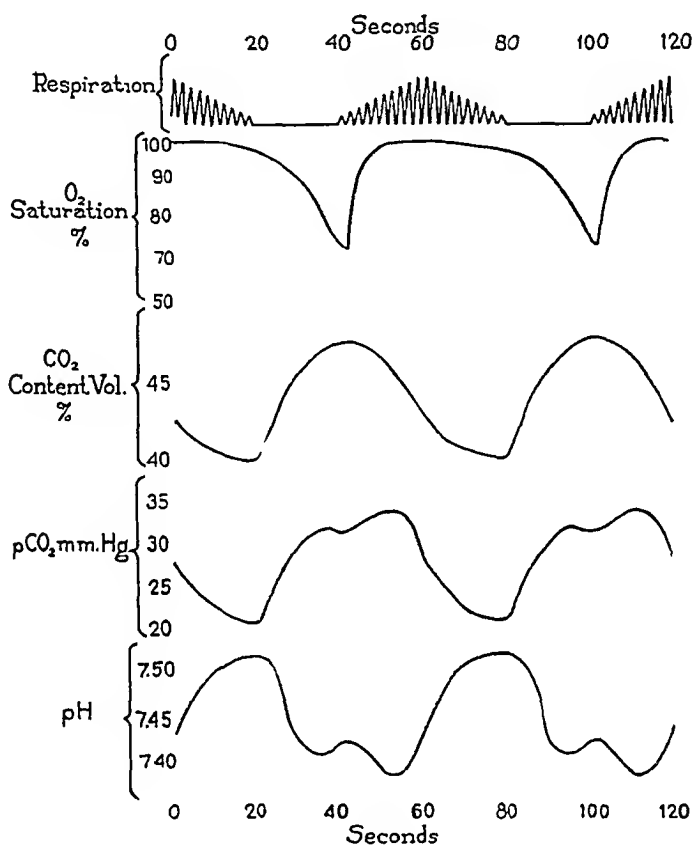
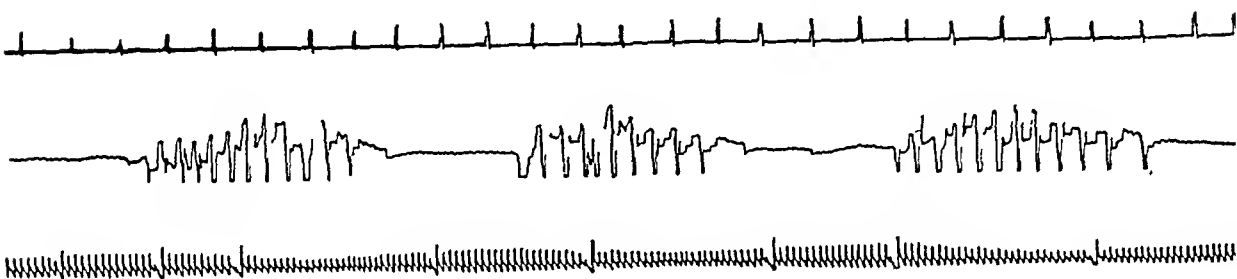


Chart 8.—The curves pass from left to right. This is a diagram and is not based on actual data but is constructed as a result of the general principles arrived at in an as yet incomplete study of the mechanism of experimental Cheyne-Stokes respiration. During apnea the carbon dioxide accumulates rapidly at first and then more slowly, while oxygen behaves in the reverse manner. During the first part of apnea the blood becomes more acid because of carbon dioxide accumulation, but toward the end of apnea there is a rapid conversion of HbO_2 into Hb and as a consequence the p_{H} tends to become more alkaline. At the onset of breathing the initial change is in carbon dioxide because of its greater diffusion velocity, but after one or two breaths there is a sudden increase in the oxygen saturation with a resulting increase in acidity of the blood. While this is taking place the breathing is crescendo. After the blood has become normally saturated with oxygen the carbon dioxide effect again predominates and further breathing causes the blood to become more alkaline. This causes the respiration to assume the diminuendo character. It is evident that the double peaks in the curves of p_{H} and $p\text{CO}_2$, which are due to the differences in the physical and physiologic characteristics of oxygen and carbon dioxide, may be important factors in the production of the characteristic periodic breathing.

tension, and furthermore, the periodic breathing is most marked at the onset of sleep, at a time when there is no primary further increase in the ventilation.

(b) Depressed Sensitivity of the Respiratory Center: The tendency of morphine and of other respiratory depressants to produce Cheyne-Stokes respiration is well recognized. Sleep is characterized by a general depression in the irritability of the nervous system, and it seems likely that the appearance of periodic breathing at the onset of sleep, both in normal persons and in patients with cardiac disease, is related to depressed sensitivity of the respiratory center. When our patients

SUBJECT A.B.



SUBJECT P.F.

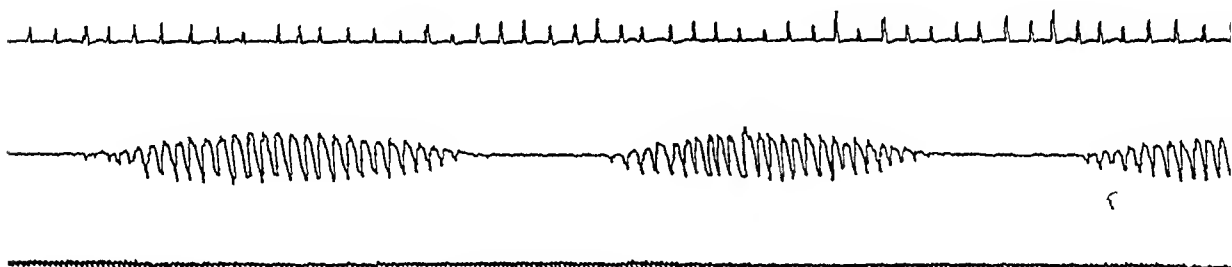


Chart 9.—The curves pass from left to right. In each tracing the upper curve represents time, the intervals being five seconds in the case of A.B., and three seconds in that of P.F. The middle curves designate respiration, and the lower curves indicate blood pressure, which was recorded by means of an Erlanger capsule attached to a blood pressure cuff placed on the subject's arm and inflated to about 100 mm. of mercury. Changes in the amplitude of the excursions reflect alterations in blood pressure. Since the blood pressure rises progressively during apnea (asphyxia) and falls during hyperpnea (relief of asphyxia), it seems that these alterations are results rather than causes of the changes in breathing.

passed suddenly into the sleeping state the breathing was immediately diminished, and usually there was total apnea.

It appears therefore that either of the two factors which have been mentioned may, acting alone, produce periodic respiration, but that in many patients both are operative, the overventilation being continuously present and the additional effect of respiratory depression at the onset

of sleep causing the phenomenon to become more pronounced. However, even though such an explanation would account for the occurrence of periodic alterations of hyperpnea and apnea, it fails to indicate the cause of the peculiar character of the hyperpneic phase, i. e., the progressive increase followed by the steady decrease in the amplitude of the respiratory movements.

6. *Observations Concerning the Cause of the Crescendo and Diminuendo Portions of the Hyperpneic Phase.*—One might suppose that the final result of reflex stimulation plus diminished sensitivity would be such as to produce something approaching normal breathing. Actually this is not usually the case for reasons which are illustrated in chart 8. This diagram does not represent actual data but is based on the general principles arrived at from data obtained by King and Harrison in a study of the mechanism of experimental Cheyne-Stokes breathing.⁸

It can be seen that during apnea the oxygen saturation diminishes slowly at first and more rapidly when the alveolar oxygen tension has decreased to a point corresponding to the steep part of the curve for oxygen dissociation. This decline continues until just after the beginning of breathing, and then the oxygen saturation abruptly rises to a normal or a supernormal level, where it remains throughout the remainder of the hyperpneic phase.

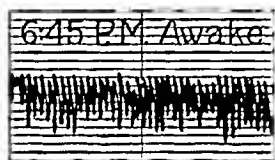
The behavior of carbon dioxide is different. As apnea begins, this gas accumulates in the blood at first rapidly and then more slowly. With the onset of breathing the carbon dioxide content begins to decrease. Because of the lesser diffusion velocity of oxygen this change sets in before the latter gas starts to increase. During the crescendo phase of hyperpnea the rate for loss of carbon dioxide increases, and then the excretion becomes slower as the breathing passes into the diminuendo phase.

These differences between the behavior of the two gases are in accord with what one would expect from the differences in their physical and physiologic properties, the changes in carbon dioxide beginning a little sooner because of its greater diffusion velocity but being gradual because its dissociation curve approaches a straight line. Oxygen, on the other hand, exhibits little change so long as the oxygen tension is in the normal region because at this point its dissociation curve is almost flat. However, when the oxygen pressure is low its dissociation curve is more nearly vertical and hence, once this point has been reached, the decrease (at the end of apnea) and the increase (shortly after the onset of breathing) in the amount of oxygen in the blood occur with great abruptness.

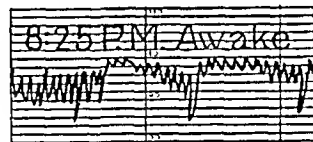
8. This study is not yet complete and will be published later.

The curve for p_H in chart 8 is of special interest. At the beginning of apnea the blood becomes rapidly more acid, but toward the end of apnea there is either no further change or a slight shift toward alkalinity. The latter phenomenon is to be attributed to the simultaneous rapid conversion of oxyhemoglobin into the less acid reduced hemoglobin. At the onset of breathing there is a slight initial rise in p_H because the carbon dioxide begins to decrease immediately. However, this is followed by a second acid peak, which occurs at the same time as, and is due to, the sudden oxygenation of the hemoglobin. Consequently, since the most acid point in the cycle occurs several seconds after the onset of breathing the respiration is crescendo. After the blood has become oxygenated, the further effect of breathing is to cause the blood

SUBJECT E.G.



SUBJECT R.P.



SUBJECT P.F.

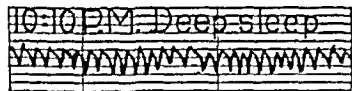
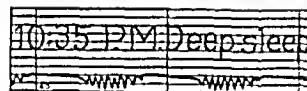
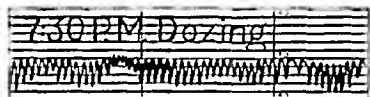


Chart 10.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The curves illustrate the type of breathing at the time when the samples of blood were drawn (table 1).

to become more alkaline from loss of carbon dioxide, and the result is the second or diminuendo portion of the hyperpneic phase. Then apnea occurs and the cycle repeats itself.

The curve for carbon dioxide tension is, as would be expected, similar to the reciprocal of the curve for p_H , the point of highest carbon dioxide tension coming not at the end of apnea but at the time of the secondary rise which occurs during the first part of hyperpnea.

The effect of the irregular behavior of the carbon dioxide tension and the p_H is to produce an "overshooting" both of hyperpnea and of apnea, and this result is of fundamental importance in the production of pronounced Cheyne-Stokes respiration. It does not seem likely that the mechanism under discussion is the sole or even the chief cause of

periodic breathing in general, but it is obvious that such "overshooting" will tend to exaggerate any preexisting tendency toward periodic breathing.

Changes in blood pressure might seem to be another possible cause of the peculiar character of the respiratory movements during the hyperpneic phase, and a number of authors have maintained that this is the case. In order to test this hypothesis we have made simultaneous tracings for blood pressure and respiratory curve, examples of which are shown in chart 9. It can be seen that the blood pressure falls during hyperpnea and rises during apnea. This indicates that the changes in blood pressure are, in the main, the result of alternate development and relief of asphyxia. Hence, it may be concluded that in the type of Cheyne-Stokes respiration under discussion, i. e., that due to congestive heart failure, the alterations in blood pressure are the result and not the cause of the change in breathing.

7. Relation Between Changes in Blood Gases and the Occurrence of Periodic Breathing at the Onset of Sleep.—Analyses of the arterial blood of three patients have been made before and after the onset of sleep. The blood was drawn at a uniform rate throughout a complete respiratory cycle, and consequently the values obtained indicate the average condition of the blood, but they do not represent the actual composition either during apnea or during hyperpnea.

In two instances the patients slept spontaneously; three times morphine was administered in order to secure sleep, but the results did not, except in one observation, differ from those obtained when no sedative was given.

The analyses were made according to the methods used in the other studies in the present series: Oxygen and carbon dioxide were measured according to the Van Slyke-Neill technic, the p_H was determined by Cullen's colorimetric method, and calculations of carbon dioxide tension were made from the Hasselbach equation, a value of 6.1 being assumed for pK^1 .

The values for the blood gases are shown in the table and the corresponding respiratory curves may be seen in chart 10. In three observations the patient was awake when the first sample was drawn. As somnolence set in, Cheyne-Stokes respiration developed in the patients who did not already have it (E. G., 12-19 and 3-2) and in the other subject (R. P.), who exhibited slight irregularity when awake, the phenomenon became more marked. Nevertheless, the two samples of blood were in each instance practically identical in composition, no alteration beyond the error of the methods used being observed in oxygen saturation, carbon dioxide pressure or p_H . Consequently, it seems justifiable to conclude that the appearance or increase in the degree of periodic breathing at the onset of sleep is not due to changes in the

composition of the blood but must be ascribed to some other factor. For reasons which have been mentioned we believe that this factor is the rather sudden decrease in sensitivity of the nervous system—and hence of the respiratory center—which occurs at the onset of sleep.

In three instances blood was obtained in the dozing state when Cheyne-Stokes respiration was present, and later during the deep sleep after the breathing had become regular. Constant differences between the oxygen and the carbon dioxide contents of the two samples were not found. In each instance, however, the p_H was measurably lower and the carbon dioxide tension definitely higher in the sample drawn during deep

Alterations in Arterial Blood Gases Associated with Sleep in Patients with Cheyne-Stokes Respiration and Cardiac Failure

Sub- ject	Date	Time	Cheyne- Stokes Respiration	Oxygen Satura- tion, per Cent	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Pressure, Mm. of Mercury	p_H	Comment
E. G.	12/19	5:00	Absent	92.9	53.8	38.3	7.40	Awake
		5:35	Mild	91.0	53.9	39.1	7.39	Dozing; morphine at 5:05 p. m.
	2/28	7:30	Mild	78.8	60.2	45.1	7.38	Dozing
		9:30	Absent	80.1	61.5	49.0	7.35	Deep sleep; no drugs
	3/ 2	6:45	Absent	95.3	62.4	43.4	7.41	Awake (chart 10)
		7:30	Mild	94.8	60.6	43.0	7.40	Dozing, after morphine 0.010 Gm.
		8:10	Moderate	95.3	60.8	43.1	7.40	Dozing
		10:35	Very marked	68.7	68.2	43.4	7.45	Deep sleep, after morphine 0.010 Gm. additional
R. P.	2/27	8:25	Mild	95.7	49.1	34.9	7.40	Awake (chart 10)
		9:10	Marked	95.2	51.1	36.2	7.40	Dozing, after morphine, 0.015 Gm. and caffeine, 0.2 Gm.
		10:10	Absent	90.3	51.4	38.1	7.38	Deep sleep
P. F.	3/29	7:15	Moderate	92.0	51.7	36.0	7.41	Dozing (chart 10)
		8:30	Absent	94.8	52.0	38.6	7.38	Deep sleep* (no drugs)

* This patient awakened while the sample of blood was being obtained; the other subjects remained asleep throughout.

sleep when the breathing was regular than in the previous sample drawn in the somnolent state when Cheyne-Stokes respiration was present.

In one patient who had to be given morphine twice in order to produce deep sleep the periodicity was progressively more marked as sleep became deeper. He exhibited no significant change in his blood in passing from the waking to the somnolent state, although the breathing became periodic. After the second dose of morphine he sank into a deep sleep; Cheyne-Stokes respiration was much more pronounced, and the blood gases exhibited striking changes, the oxygen decreasing, the carbon dioxide content increasing and the p_H rising, but the carbon dioxide tension remaining unchanged.

These observations indicate that the disappearance of Cheyne-Stokes breathing during deep sleep—unlike its appearance during light sleep—

is associated with slight but detectable chemical changes in the arterial blood in the direction of increased acidity and higher carbon dioxide tension. These chemical alterations have been described by others⁹ and appear to be a characteristic feature of normal sleep. It seems possible that since overventilation can produce Cheyne-Stokes respiration the disappearance of the periodicity during deep sleep is due to decreased ventilation of the blood with consequent increase in acidity and carbon dioxide tension.

On the other hand, during deep sleep, the periodic breathing may instead of disappearing become exaggerated, and in such an instance, as increasing respiratory depression occurs, apnea becomes longer, and marked oxygen unsaturation develops. The anoxemia results in "overshooting" of the respiration during the next hyperpneic phase because of the mechanism which has been described (increase in acidity at the onset of breathing due to sudden oxygenation of hemoglobin), and this in turn, by making the blood more alkaline, tends to keep the carbon dioxide tension from rising as it normally does during sleep. Hence, the paradoxical condition of the blood—which is overventilated as regards carbon dioxide and insufficiently aerated in respect to oxygen—persists, and this in combination with the depressed sensitivity of the respiratory center causes the periodic breathing to assume and maintain its exaggerated form.

COMMENT

As a result of the data herein reported we are now in a position to return to our original problem, i. e., the cause of the dyspnea appearing at the onset of sleep.

A patient without cardiac disease may have striking Cheyne-Stokes respiration and yet suffer no subjective respiratory distress, provided he has a normal vital capacity. It has been pointed out elsewhere in these studies that dyspnea is inversely proportional to the vital capacity and directly proportional to the ventilation. Patients with congestive heart failure have diminished vital capacities, and consequently anything which produces marked increase in ventilation tends to cause subjective respiratory distress but only during the time in which the ventilation is increased. Therefore a patient with Cheyne-Stokes respiration and cardiac failure suffers from dyspnea only during the hyperpneic phase and has no distress during apnea. We do not intend to state that dyspnea occurs because of increased ventilation, but we mean to state that both the subjective distress and the augmented breathing are parallel responses (the one cortical and the other medullary) to the same under-

9. Bass and Herr, quoted by Kleitman: *Physiol. Rev.* **9**:624, 1929. Kunz, J.: *Ztschr. f. d. ges. exper. Med.* **59**:248, 1928. Endres, G.: *Biochem. Ztschr.* **142**: 53, 1923.

lying causes, and hence the ventilation may be used at any given level of vital capacity, as a measure of the dyspnea.

The lowered vital capacity is the predisposing cause of the type of dyspnea under consideration, and the increased ventilation is the precipitating factor. It has been shown that the increase in ventilation is a manifestation of periodic breathing, which in turn is a complex phenomenon produced by a combination of a number of factors.

This concept appears to us to account satisfactorily for various clinical phenomena which have been observed, of which the following are examples: 1. Patients with severe congestive heart failure often have repeated "flurries" of dyspnea when awake and then have severe attacks on going to sleep. In those patients overventilation alone may produce Cheyne-Stokes breathing which becomes suddenly worse at the onset of sleep.

2. Patients with less severe congestive failure may have their seizure only on going to sleep. In such instances the overventilation alone is not sufficiently severe to produce marked periodicity, but when the added factor of respiratory depression is present, Cheyne-Stokes breathing becomes pronounced.

3. Attacks of dyspnea of the type under consideration are most common in elderly persons, who are especially subject to arteriosclerotic and hypertensive cardiac disease, which impose an initial strain on the left ventricle, and hence lead to overventilation from pulmonary congestion. Furthermore, the sensitivity of the respiratory center is probably less in older subjects with normal hearts, as evidenced by their tendency to periodic breathing.

4. Any stimulus which wakens a patient is likely to precipitate a paroxysm of dyspnea. The sudden increase in respiratory sensitivity as a result of awakening causes overventilation.

5. Once a patient passes the dozing stage and becomes deeply asleep he is likely to have no further periodic breathing. At the onset of sleep the decrease in respiratory sensitivity which tends to precipitate Cheyne-Stokes breathing comes suddenly, but the rise in carbon dioxide tension which is secondary to the diminished ventilation develops gradually and tends to prevent further attacks by abolishing apnea.

SUMMARY

A pneumographic study has been made of patients complaining of attacks of dyspnea coming at the onset of sleep. Such patients exhibit Cheyne-Stokes respiration, which either appears or becomes more marked at the onset of sleep, and later during deep sleep either disappears or becomes less marked. As sleep develops, respiratory periodicity occurs with increasing length of the apneic intervals and a

corresponding increase in the intensity of the hyperpneic phase, which eventually becomes so marked as to awaken the patient and cause dyspnea.

An investigation has been made concerning the underlying factors responsible for these phenomena, and it is concluded that the main causative agents are (1) overventilation due to reflex respiratory stimulation from congested lungs, and (2) respiratory depression occurring at the onset of sleep. Acting singly or in combination these two physiologic alterations appear to be responsible for the periodic breathing. The associated violent hyperpnea in a patient with diminished vital capacity is responsible for the subjective respiratory distress.

Certain observations on the blood gases before and during sleep have been presented, and these are compatible with the hypothesis mentioned. The development of periodic breathing is usually not associated with significant alterations in the composition of the blood. As sleep continues there is, however, a demonstrable increase in the carbon dioxide tension and in the acidity of the blood, and coincidentally the respiration becomes regular.

The alterations in the blood gases are primarily effects of the changes in breathing. However, as a result of the alteration in the blood, the breathing undergoes further changes which lead to the production of the characteristic paroxysmal seizures of respiratory distress.

CONGESTIVE HEART FAILURE

XXI. OBSERVATIONS CONCERNING THE MECHANISM OF CARDIAC ASTHMA

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DEFINITION

The term "cardiac asthma" has been employed by different authors to designate various things. According to certain writers it includes any seizure of paroxysmal dyspnea occurring in a patient with cardiac disease. Other investigators restrict its use to attacks in which at the time of seizure there are auscultatory phenomena similar to those heard in bronchial asthma, i. e., coarse, squeaking, musical or sonorous râles. As used in this and in the future studies of the present series, the term cardiac asthma refers to paroxysms of dyspnea which (1) occur in patients with passive congestion of the lungs secondary to failure of the left side of the heart, (2) usually wake the patient from sound sleep but occasionally occur during the waking hours, (3) sometimes terminate in acute edema of the lungs, (4) are often but not necessarily precipitated by coughing, and (5) are not ordinarily associated with Cheyne-Stokes respiration. In many patients with this condition "asthmatic" râles can be heard over the lungs during the attack. Cardiac asthma does not refer to paroxysmal dyspnea associated with periodic breathing, to dyspnea developing gradually in the afternoon and evening, to attacks of bronchial asthma occurring in persons with right ventricular failure or to acute pulmonary edema appearing as a terminal manifestation in moribund persons without structural cardiac disease.

The various hypotheses which have been advanced to explain the mechanism of cardiac asthma have been reviewed in a previous paper,¹ and it was pointed out that there is no generally accepted theory. It has seemed to us that the results of our observations concerning other kinds of nocturnal dyspnea might serve as a starting point for a further investigation of the subject. All types of cardiac dyspnea which have

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1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, *Arch. Int. Med.* **53**:561 (April) 1934.

so far been studied have been shown to be related to two fundamental underlying factors: (a) diminished respiratory reserve because of decreased vital capacity and (b) reflex stimulation of the respiration. Both of these factors are present during the interval between attacks, for patients with cardiac asthma regularly show both abnormally low vital capacity and abnormally great ventilation. Examples are shown in table 1 of our previous article concerning orthopnea.² Subjects A. C., E. G. and C. M. were studied during attacks of cardiac asthma, and subjects P. H., D. W. and W. J. had attacks, but the observations on them shown in the table were made between seizures. All of these patients had subnormal vital capacities and abnormally great ventilation. Furthermore, the data on the blood gases in the same table indicate that attacks of cardiac asthma are due neither to insufficient aeration of the arterial blood nor to diminished cerebral blood flow, because the three patients mentioned, who were studied during seizures, did not show significant abnormalities either in the arterial blood or in the blood obtained from the internal jugular vein.

Patients with cardiac asthma have pulmonary congestion which has two effects: a decrease in vital capacity and reflex stimulation of respiration. The recent studies of Weiss and Robb,³ who found that the vital capacity, which was diminished between the seizures, underwent further decline during the attacks, indicate that the degree of pulmonary congestion is increased at the time of the seizures. If we assume, as a working hypothesis, that the underlying cause of cardiac asthma is congestion of the lungs, it is evident that certain questions must still be answered before we can have a clear concept of the mechanism of the syndrome. These include: 1. What is the cause of the greater degree of pulmonary congestion during sleep? 2. What

2. Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. L., and Tims, M. M.: Studies in Congestive Heart Failure. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, *J. Clin. Investigation* **10**:833 (Oct.) 1931.

3. Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea), *J. A. M. A.* **100**:1841 (June 10) 1933. This important study on the subject of cardiac asthma was published since the present article was written. These authors found that the attacks were characterized by an acute increase in the degree of pulmonary congestion. No constant abnormalities in the cardiac output per minute were found either during or between the seizures. Measurements of volume of the lungs revealed a state of acute functional emphysema dependent on engorgement. The vital capacity was decreased during the seizures. Vagal reflexes were demonstrated to be an important factor in the production of dyspnea, which was benefited in several instances by blocking the vagus nerves with procaine hydrochloride. The essential mechanism of the seizures was believed to be the coexistence of subacute left ventricular failure and acute precipitating factors. Our conclusions are, in general, in accord with those of Weiss and Robb.

is the relation between cardiac asthma and acute pulmonary edema? 3. Why do many patients with cardiac asthma exhibit auscultatory phenomena similar to those heard in bronchial asthma? 4. Why does morphine have a beneficial action in preventing and combating the seizures? The following studies were carried out to gather data concerning these questions.

RESULTS

Effect of Morphine on Respiratory Measurements and on Blood Gases in Patients with Cardiac Asthma.—In order to determine whether or not there was an increased degree of pulmonary congestion during the seizure we made attempts to measure the vital capacity and the ventilation during and after the attack. In order to be certain that the two observations could be made within a short time of each other morphine was given immediately after the first studies had been made, and the investigations were repeated from thirty to forty minutes after administration of the drug; by that time the patient's dyspnea had usually diminished or disappeared. Measurements of ventilation and of vital capacity were made, and in addition samples of arterial blood were obtained and analyzed by the methods used in the other studies of this series (carbon dioxide and oxygen with the Van Slyke apparatus, p_H by Cullen's method and carbon dioxide tension by calculation from the Hasselbach formula, using a value of 6.1 for pK^1).

The data are shown in table 1. During the seizure the vital capacities were considerably lower and the ventilation much greater than normal. We have repeatedly measured the resting ventilation per minute of normal subjects under similar conditions and have found values ranging from 3.5 to 6 liters, whereas, during the seizures of cardiac asthma the values for the patients were between 7.4 and 14.1 liters per minute. Similarly, normal adults usually have vital capacities of from 3 to 5 liters, whereas the vital capacities of the patients were usually considerably less than this.

Following the administration of morphine six of the seven subjects experienced relief, relative or absolute, from dyspnea. In each of the six there was a well marked decrease in ventilation. The seventh patient said that his dyspnea was no better, and he failed to show any decrease in ventilation. This patient's vital capacity was lower after he had received morphine; three subjects exhibited a definite although slight increase in vital capacity, and two subjects exhibited no significant change in this function. The latter two passed into a state of sound sleep after receiving morphine and had to be aroused repeatedly in order that vital capacities might be measured.

During the dyspneic seizure the respirations were usually faster than normal, and in every case the rate of breathing was slower after

medication, this effect being least pronounced in the patient J. P. whose subjective distress was not relieved.

Analyses of the arterial blood taken during the attack of dyspnea revealed no constant abnormalities. One patient who also had acute pulmonary edema had marked anoxemia, and this man's arterial satura-

TABLE 1.—*Effect of Morphine on Blood Gases and on Respiratory Movements*

Subject	Date, 1931	Conditions	Oxygen Saturation, per Cent	Serum Carbon Dioxide, Volumes per Cent	Serum Carbon Dioxide Tension Mm. of Mercury	Serum p_{H}	Vital Capacity, Liters	Ventilation per minute, Liters	Ventilation Vital Capacity	Respiration per Minute	Comment *
J. D.	10/15	Before morphine	100.0	59.7	39.0	7.43	2.04	14.1	6.91	48	Dyspnea, severe
		After morphine	99.3	62.8	42.7	7.42	2.10	11.6	5.50	25	
E. G.	10/15	Before morphine	92.8	51.4	26.9	7.54	2.49	13.4	5.33	33	Dyspnea, severe
		After morphine	91.9	52.5	36.5	7.41	2.65	9.9	3.72	17	
W. L.	11/ 2	Before morphine	56.4	74.0	44.1	7.48	10.5	31	Acute pulmonary edema
		After morphine	80.1	73.3	41.8	7.50	7.8	27	Dyspnea, very severe
B. S.	12/15	Before morphine	92.4	54.8	40.7	7.38	2.24	10.1	4.52	15	Dyspnea, mild
		After morphine	92.0	56.1	40.9	7.39	2.37	8.5	3.59	12	
S. U.	12/19	Before morphine	60.0	43.6	7.39	3.30	7.4	2.26	23	Dyspnea, mild; venous blood
		After morphine	57.4	41.7	7.39	3.48	5.5	1.59	15	Dyspnea, mild; venous blood
M. G.	12/19	Before morphine	2.08	12.7	6.11	26	Dyspnea, moderate
		After morphine	2.05	6.7	3.26	20	
J. P.	12/30	Before morphine	86.0	66.2	44.2	7.45	1.90	10.2	5.33	17	Dyspnea, severe
		After morphine	84.0	67.2	43.9	7.44	1.70	10.1	5.94	15	Not helped by morphine

* In all the patients except in the last one the dyspnea was less severe after morphine had been administered.

tion rose from 56 per cent before to 80 per cent after the administration of morphine. The other patients had values ranging from 100 to 86 per cent for the arterial oxygen saturation during the paroxysm, and relief from the dyspnea by morphine was not associated with significant changes.

Similarly, the values for carbon dioxide content of the arterial serum were all within normal limits during the dyspneic seizure and were not

altered in any constant direction by morphine. In five patients the p_H was likewise within the normal range during the attack; the sixth had a tendency toward alkalosis (p_H 7.54). In the last subject relief from dyspnea by morphine was associated with a decrease of 0.13 in p_H and an increase of approximately 10 mm. in carbon dioxide tension. Other subjects exhibited no significant changes in p_H after they received morphine. Likewise the carbon dioxide tension exhibited no constant alterations, the only striking change being in the subject mentioned who had, during the paroxysm, an abnormally low carbon dioxide tension, whereas the values for the other patients were within the normal range.

It is evident from these data that the dyspnea of cardiac asthma cannot be primarily attributed to insufficient aeration of the arterial blood, although anoxemia may be an important added factor when acute pulmonary edema supervenes. Except in patients with pulmonary edema, morphine does not usually produce significant changes in the composition of the arterial blood. Occasionally, relief from dyspnea may be associated with decided increase in the acidity of the blood.

These conclusions are in general agreement with those of other authors. Eppinger, von Papp and Schwarz⁴ found that their dyspneic patients usually had normal values for carbon dioxide pressure and p_H , whereas anoxemia of marked degree occurred only in subjects with edema of the lungs or other pulmonary disorders. Fraser⁵ reported low values for carbon dioxide tension and hydrogen ion concentration of the arterial blood in the majority of his dyspneic patients, but noted that patients with pulmonary edema had anoxemia. He likewise studied patients before and after the administration of morphine and observed that in some instances this drug, although relieving the dyspnea, caused the carbon dioxide tension to increase and the oxygen saturation to decrease.

It appears, therefore, that the precipitating causes of the attacks of cardiac asthma do not act by altering the composition of the blood but by influencing the vital capacity and the ventilation.

Importance of cough as a Precipitating Cause of Paroxysmal Dyspnea.—Patients with paroxysmal cardiac dyspnea may be classified in three groups with regard to their cough: 1. Subjects who have characteristic paroxysmal nocturnal dyspnea with little or no cough. With this group of patients we are not, for the present, concerned.

4. Eppinger, H.; von Papp, L., and Schwarz, H.: *Das Asthma cardiale*, Berlin, Julius Springer, 1924.

5. Fraser, F. R.; Harris, C. F.; Hilton, R., and Linder, G. C.: *Quart. J. Med.* 22:1, 1928.

2. Patients who state that they wake up and feel short of breath and later begin to cough, thereby becoming more short of breath.

3. Persons who have coughing "spells" and then begin to feel dyspneic. The paroxysms may occur when the subject is awake but are likely to be more severe during the night, awakening the patient from sleep. Patients in this group insist that while at rest they have no dyspneic seizures other than those which are preceded by coughing. Observation during the attacks confirms their statements. While breathing quietly they begin to cough and after cessation of the cough the respirations remain rapid and labored for a time and then gradually return to the previous rate and character. During and immediately after the coughing seizure striking venous distention and outspoken cyanosis may develop.

The following cases are illustrative of the importance of cough as a precipitating factor in causing attacks of paroxysmal dyspnea.

CASE 1.—M. S., a white housewife, aged 63, suffered from frequent attacks of bronchitis for many years. Dyspnea on exertion had been progressive during the past ten years, and for five years she had had occasional paroxysms of coughing in the day and, during the night, frequent severe seizures which would wake her from a sound sleep. After the coughing began she would feel short of breath. Eventually she would expectorate a small amount of mucopurulent sputum, and her coughing would cease abruptly but her dyspnea would last for a number of minutes longer, then gradually decrease and finally disappear. For three months there had been progressive swelling of the feet and abdomen.

Examination revealed undernurtition, marked cyanosis, slight clubbing of the fingers, venous distention, moderate cardiac enlargement to the right and left, an accentuated second sound in the pulmonic area and typical signs of emphysema, bronchitis and bronchiectasis. There was no orthopnea. The liver was markedly enlarged and there were signs of free fluid in the abdomen. The electrocardiogram revealed right ventricular preponderance. The patient was observed for ten days in the hospital and during this period never complained of dyspnea except during or after a paroxysm of coughing. Every attack of coughing which lasted for more than a few seconds was accompanied by some dyspnea. There were mild seizures during the day, but the most severe attacks came at night after she had been asleep for two or three hours.

This patient showed a typical case of cardiac failure secondary to chronic pulmonary disease (cor pulmonale, pulmonary hypertension). Her dyspneic seizures were due to her cough. However, she could not be considered as having cardiac asthma because clearly her dyspnea was originally of pulmonary origin, and cardiac failure developed secondarily.

CASE 2.—M. G., a Negress, aged 42, was first seen in July, 1928, complaining of cough and of paroxysmal dyspnea which would wake her from a sound sleep. At this time she was found to have hypertension, marked cardiac enlargement, gallop rhythm, and a few râles at the bases of the lungs. Following medication

with digitalis and no other treatment, she became free from symptoms and remained so for two years, except for dyspnea on climbing stairs and some nocturnal seizures during very hot weather. During the last two years her cough had become much worse. In December, 1931, she had a second frank break in compensation and had to be readmitted to the hospital. Her blood pressure was still elevated. There were scattered dry, piping râles throughout both lungs and moist râles at the bases of the lungs. She was observed during the attacks of dyspnea; these sometimes came on during the late afternoon or early evening while the patient was awake, particularly when the room was unusually warm, but usually they occurred after she had been asleep for an hour or more.

While still asleep she would begin to cough and then, on awakening, the cough would become more violent, and she would complain of dyspnea. Her seizures always began with cough, and during the attacks there would be a greater number of moist and dry râles in the lungs. Morphine always gave relief.

In this patient hypertension caused pulmonary congestion which later was complicated by bronchitis. Coughing precipitated her attacks of dyspnea. The majority of patients with cardiac asthma present clinical pictures somewhat similar to this one.

CASE 3.—J. P., a Negro, aged 49, began to have dyspnea on exertion six months before admission. One month later he began to have attacks of paroxysmal dyspnea at night; these usually started after 8 p. m., lasted thirty or forty-five minutes, were usually preceded by a "rattling or wheezing" in the throat and often by a severe attack of coughing. During this time the patient would sit upright, cough, become quite dyspneic and spit up tenacious sputum. After a number of minutes the attacks would cease. Gradually the seizures became more frequent, and for the past two weeks they had troubled him much more than usual. He had slight palpitation during the attacks. There had been no edema of the ankles and no precordial pain.

Examination revealed a tall, thin, but well developed Negro, who could lie flat in bed without dyspnea at the time. The lungs showed numerous coarse, scattered râles over the middle of each side of the chest in the back. These tended to clear after cough. The heart was enlarged and the rate increased; the sounds were forceful, and infrequent extrasystoles were present. The second aortic sound was accentuated. A faint, early blowing diastolic murmur was heard down the middle of the sternum and at the apex, where there was also a presystolic gallop. The pulse was rapid and full, not definitely of the Corrigan type. The blood pressure was 146 systolic and 92 diastolic, and pulsus alternans was noted. The liver was not felt, and there was no pitting edema. The Wassermann reaction was positive. A diagnosis of syphilis of the aorta with aortic insufficiency was made.

While in the ward the patient had several attacks of paroxysmal dyspnea. His chest had been examined immediately before one of these attacks, and at that time his lungs were clear. He was lying in a semirecumbent position and was only slightly short of breath. In order to observe the effects of coughing a face mask was attached, and after several minutes, during which the expired air was collected, he was instructed to cough violently. Within two minutes after he had started coughing he suddenly sat straight up in bed, became markedly dyspneic, broke out in profuse perspiration, continued to cough and expectorated a moderate amount of frothy sputum; after about ten minutes the attack gradually ceased. During

the attack moist râles were audible throughout the lower portion of the chest, but these soon cleared up. Under rest in bed, medication with digitalis and sedatives the attacks ceased and he improved.

This patient illustrates the effect of cough in producing marked dyspnea associated with the sudden development of pulmonary edema.

In order to obtain objective data concerning the effect of coughing on breathing the ventilation was measured in a number of patients before, during and after coughing. For this purpose a face mask and a Tissot spirometer were used. The patient sat quietly in a comfortable chair for fifteen minutes or longer, and the face mask was then applied. After a further preliminary period the resting ventilation was measured for three successive minutes. The subject was then instructed to cough every ten seconds. This was kept up for three minutes. During the

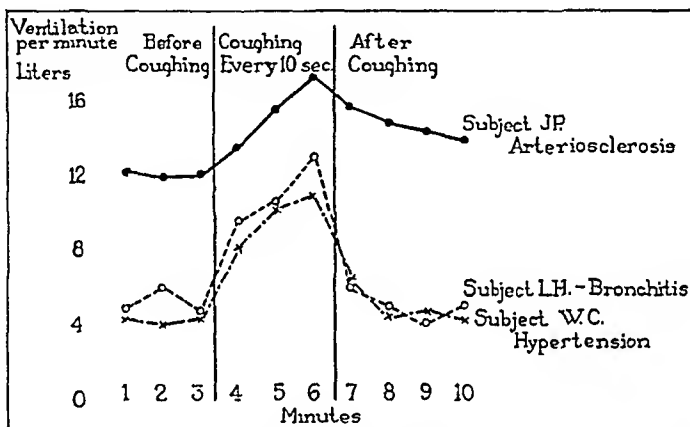


Fig. 1.—The upper curve represents the ventilation of a patient with mild congestive heart failure; the two lower curves are from patients who were ambulatory and free from symptoms at rest but had some dyspnea on exertion. Voluntary coughing produced an increase in the ventilation in each subject, caused slight dyspnea in L. H. and W. C., and resulted in marked dyspnea in the case of J. P., who was already slightly dyspneic before coughing. After coughing had ceased the ventilation of the two patients with compensation returned to normal rapidly, but the ventilation of the patient with decompensation remained elevated for several minutes. The curves showing the effect of coughing on the ventilation are similar to other curves obtained following any type of muscular exertion in patients with cardiac disease.

coughing and for the subsequent four minutes after coughing had ceased further measurements of ventilation were made.

In figure 1 are plotted examples of the results obtained. The upper curve represents data on a subject with decompensation who was slightly short of breath at rest. The two lower curves are obtained from ambulatory subjects who had dyspnea on walking rapidly but not at rest. It is to be noted that coughing caused a marked and progressive

rise in ventilation in each patient. L. H. and W. C. both felt slightly short of breath during and immediately after coughing. J. P., who was already slightly dyspneic at rest, complained of marked respiratory distress during and for several minutes after coughing. It is to be noted that the ventilation of the ambulatory patients remained above the resting level for about a minute after coughing stopped while the respiratory minute volume of the patient with decompensation was still elevated four minutes after the cessation of coughing.

In figure 2 are shown respiratory tracings from a normal subject and from two patients with congestive cardiac failure. Following voluntary coughing for one minute the normal person had a slight increase in respiratory rate which gradually returned to normal. In both of the patients the coughing was involuntary, coming on in one subject following a deep breath and beginning spontaneously in the other patient. It is to be noted that the increase in respiratory rate was much more pronounced in both patients who experienced dyspnea during and after the coughing than in the normal subject who experienced no dyspnea.

It is a common clinical experience that a deep breath, particularly if associated with forced expiration, is likely to be followed by coughing. In measuring vital capacities one frequently finds that each maximal expiration is followed by a short paroxysm of coughing, which is often attended and followed by an increase in the degree of preexisting dyspnea. These events are illustrated by figure 3. All of the tracings were made from the same patient, a man with congestive cardiac failure secondary to syphilitic aortic insufficiency. A maximal inspiration followed by a maximal expiration resulted in coughing, rapid breathing and dyspnea. His respiratory distress gradually subsided, and a few minutes later the respiratory rate was the same as at the beginning of the observations. A deep breath again precipitated coughing and dyspnea. He was then given 0.015 Gm. of morphine subcutaneously, and fifteen minutes later the observations were repeated. In this instance deep breathing did not initiate coughing; the respirations did not become accelerated, and no dyspnea developed. Morphine, by depressing the reflex excitability, had broken the vicious cycle.

The foregoing histories of cases and respiratory curves indicate that in certain patients with congestive heart failure coughing plays an important rôle in initiating seizures of paroxysmal dyspnea and that in other patients who are already dyspneic coughing increases the degree of respiratory distress. These facts are readily explainable when one remembers that patients of this type nearly always suffer from dyspnea on the performance of muscular exercise, and that a cough is a rather violent muscular effort. In a preceding study of

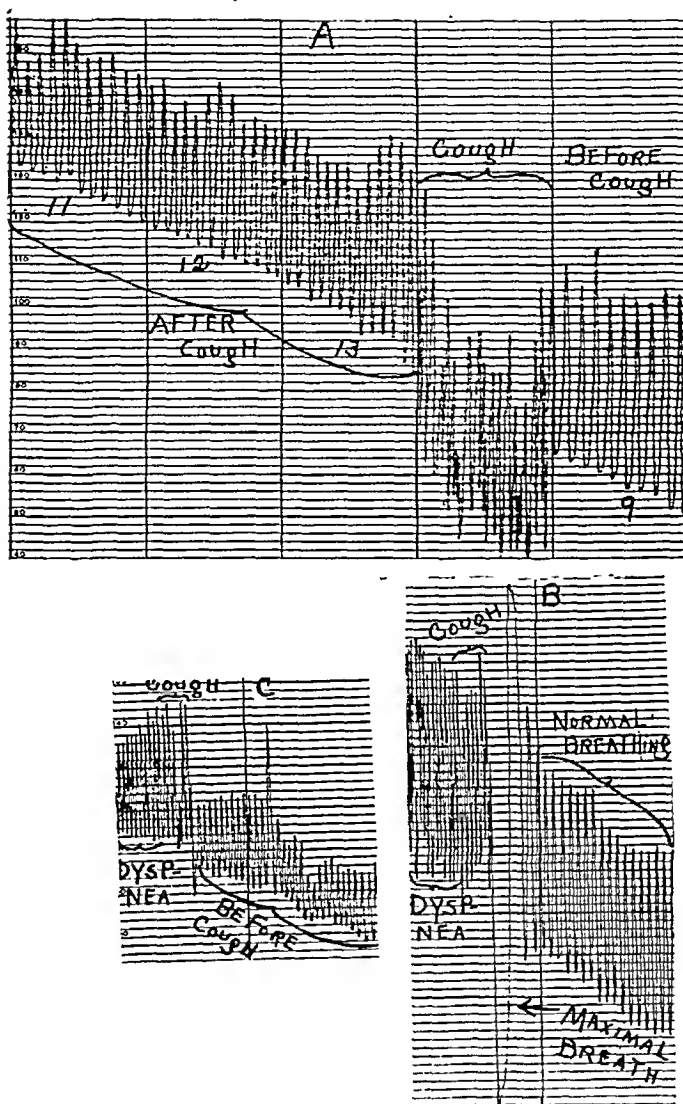


Fig. 2.—The curves all pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers below the tracing in part *A* refer to respiration per minute. The upper tracing (*A*) was obtained from a normal subject who was instructed to cough for one minute. A well marked increase in respiratory rate and a slight temporary increase in depth of breathing occurred after cessation of the cough. The lower tracing on the right (*B*) illustrates involuntary cough as a result of a deep breath and maximal expiration in a patient with mild congestive cardiac failure. Following the coughing there was a marked increase in breathing, and the subject felt short of breath. The lower tracing on the left (*C*) was made from a patient with mild congestive cardiac failure during a mild seizure of nocturnal dyspnea. The cough occurred spontaneously, and immediately afterward there was a marked increase in the rate and depth of breathing, with rather severe dyspnea.

the present series⁶ it was shown that muscular movements cause reflex stimulation of breathing. Hence, in this way cough tends to produce dyspnea. Furthermore, the act of coughing may cause a rather great temporary increase in consumption of oxygen (as much as 50 per cent in some of our cases) and this would obviously tend to increase the work of the heart and hence to aggravate the underlying condition responsible for the dyspnea.

However, there is another effect of cough which is probably even more important. In the previous study which has been referred to it was shown that increase of pressure in the right auricle and in the cardiac ends of the great veins caused reflex stimulation of breathing. Any form of muscular exercise probably tends to cause a rise in venous

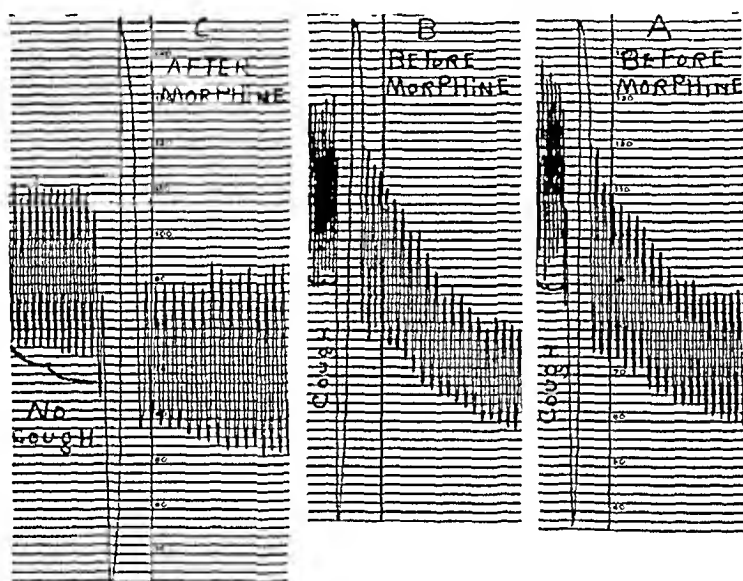


Fig. 3.—The curves pass from right to left. All of the tracings were made from the same patient, a man with congestive heart failure and nocturnal dyspnea. The right (A) and center (B) curves illustrate the occurrence, following a deep breath, of cough and increased breathing which were associated with dyspnea. Morphine was administered, and a few minutes later another tracing was made. A deep breath no longer caused coughing. The respirations did not increase, and the patient felt no dyspnea.

pressure, but coughing is especially important in this regard because during coughing there is a rise in the intrathoracic pressure with resulting distention of the extrathoracic veins. Hence, at the beginning of each inspiration following coughing there is a sudden inflow of blood into the right auricle with a resultant rise of pressure in that chamber.

6. Harrison, T. R.; Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Heart Failure: XVII. The Mechanism of Congestive Dyspnea on Exertion, *Arch. Int. Med.* **50**:690 (Nov.) 1932.

Probably because of this fact coughing has a greater effect on breathing than other muscular effort of comparable degree.

Furthermore, it has been shown⁶ that a given muscular effort produces a greater rise in venous pressure and in ventilation in a person with congestive heart failure than in a normal subject. That this is true of the muscular effort of coughing is illustrated in figure 2, in which it can be seen that the degree of increase in respiratory rate following coughing was much greater in the two patients than in the normal subject.

It is also possible that the mechanical effect of coughing may be such as to interfere with exchange of gas in the lungs and hence to add a chemical factor to the reflex influence tending to produce dyspnea. We have made no observations on this point.

As has been stated, the paroxysms of cough may come in the day but are more likely to begin during sleep and to wake the patient. One reason for this seems obvious. If, owing to pulmonary congestion, bronchitis or both conditions, there is an increase in the amount of bronchial secretion, the patient is likely to expectorate it in small amounts at frequent intervals during the day, each expectoration being accomplished by a short fit of coughing. During sleep, on the other hand, the reflex irritability of the nervous system is depressed, and consequently a greater amount of mucus accumulates before the cough reflex is elicited. However, once coughing begins, it wakes the patient, and the waking is associated with an increase in reflex irritability. Hence, the cough becomes severe and causes an increase in ventilation which, in a person whose respiratory reserve (vital capacity) is already low, is associated with dyspnea. The sequence of events in such instances is similar to that which occurs in any disease associated with cough and expectoration in persons who do not have cardiac disease, the only difference being that the latter subjects are less likely to have dyspnea because their vital capacities are greater and also because coughing does not, for the reasons already mentioned, cause as great an increase in ventilation in such persons as in subjects who have congestive heart failure. However, the difference is qualitative only, for severe paroxysms of cough such as occur in whooping cough, for instance, may cause dyspnea in persons who have normal hearts. In the case of the patient with congestive heart failure it requires less coughing, just as it requires less walking, to produce dyspnea.

It was pointed out (figs. 2 and 3) that, not only does coughing increase the breathing, but that deep breathing, especially forced expiration, tends to bring about coughing. Thus a vicious cycle may develop, the patient's attack beginning with either dyspnea or cough, and each symptom aggravating the other, the situation becoming continually

worse unless relieved either by the administration of a sedative or by expectoration of mucus.

The results obtained by measures which suppress the cough offer a further illustration of the importance of this "trigger" factor. We have occasionally seen paroxysmal dyspnea of the type in question benefited by inhalations of steam and have often seen the attacks abolished by cough syrups containing codeine, although in severe cases morphine may be necessary.

Other Precipitating Causes of Paroxysmal Dyspnea.—Cough has appeared to be the most common and most important of the precipitating causes of the dyspneic attacks in the majority of our patients. However, it is not the only factor which may start the seizures. During the patient's waking hours any stimulus which increases the ventilation

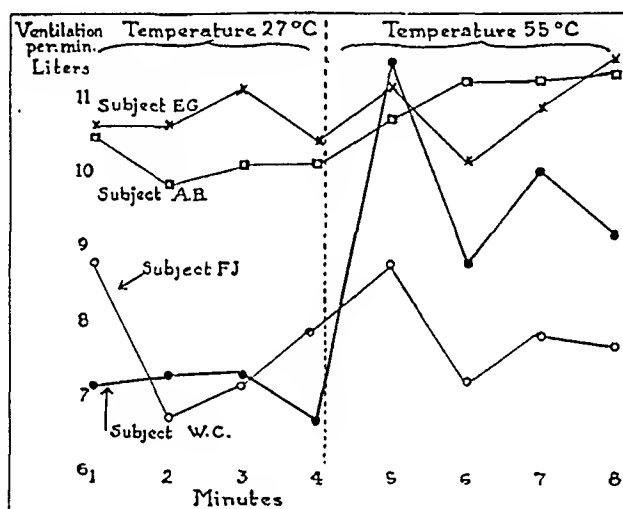


Fig. 4.—The subject rested on a couch in a warming cabinet. The ventilation was first determined at room temperature (27 C.), and then the temperature of the cabinet was increased to 55 C. by means of electric lights. The head remained outside of the cabinet. Two of the subjects showed a definite increase in ventilation, whereas the remaining two did not. This inconstancy of response is in keeping with the fact that heat is a precipitating cause of cardiac asthma in some persons and not in others.

may initiate an attack of dyspnea. Such stimuli are doubly effective if they happen to awaken the patient from sleep because then there is the added factor of the sudden increase in the sensitivity of the nervous system (and hence of the respiratory center) which occurs on passing from the sleeping to the waking state. In our patients attacks of cardiac asthma have been precipitated by such widely varying factors as nightmares, hunger, very hot weather, abdominal distention, constipation and the desire to urinate. Observations concerning the effects of some of these stimuli on breathing have been made, and examples of the results are shown in figures 4, 5 and 6. The action of an increase in

the environmental temperature was studied by placing the patient in a warming cabinet and, after measuring the ventilation at room temperature, repeating the observations with the temperature of the cabinet increased to 55 C. The head remained outside of the cabinet. As can be seen in figure 4, some persons reacted with an increase in ventilation while others did not.

The effect of fear was studied by making noises, breaking glassware, dropping tin pans on the floor, etc., while the ventilation was being measured. In figure 5, it is shown that apprehension caused a well marked increase in the ventilation in each of four subjects. It seems probable that nightmares, associated as they are with severe apprehension, have a similar effect on breathing. Such an increase in ventilation in a patient who, because of congested lungs, is already at the threshold of dyspnea will result in respiratory distress.

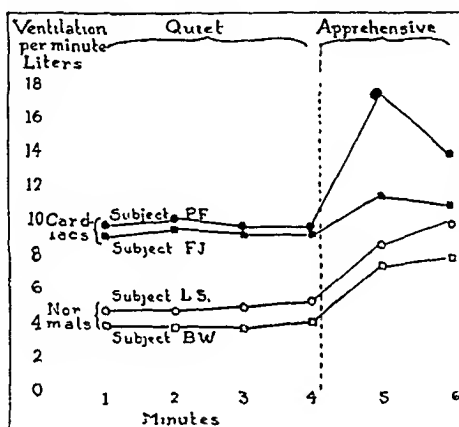


Fig. 5.—After the ventilation had been measured during resting conditions the subject was frightened by noises which were produced by slamming doors, breaking glassware and dropping tin pans on the floor, and by altercations between the operators. All the subjects remained at rest but each showed well marked increase in ventilation, and at the end of the observation each admitted that he had been frightened by the noises. It is assumed that unpleasant dreams have a similar effect on ventilation.

In order to learn something concerning the effects of distention of abdominal viscera on respiration, experiments have been made on dogs. It has been found that some animals react regularly with faster breathing and increased ventilation to the introduction of fluid into the bladder or into the rectum. Other dogs have shown less constant effects. Examples of the type of results which have been obtained are shown in figure 6. It can be seen that the introduction of 50 cc. of saline solution into the bladder caused a definite increase in respiration. Similar effects were produced in another animal by distending the colon with 100 cc. of barium sulphate paste. Up to the present time

the observations are incomplete, as the afferent path of the reflex which is probably concerned has not yet been determined. Complete observations along this line will be published at a later date, but it seems justifiable to conclude at present that distention of the bladder or colon may produce an increase in breathing.

Relation of Acute Pulmonary Edema to Cardiac Asthma.—Any attempt at a satisfactory understanding of the pathogenesis of cardiac asthma necessarily involves an explanation of the mechanism of acute edema of the lungs, which is an integral and fearsome feature of the seizures in many patients. That the underlying cause of acute pulmonary edema is failure (i. e., dilatation) of the left side of the heart is clearly indicated by the observations at necropsy in such cases, as well as by the classic experiments of William H. Welch,⁷ who produced acute

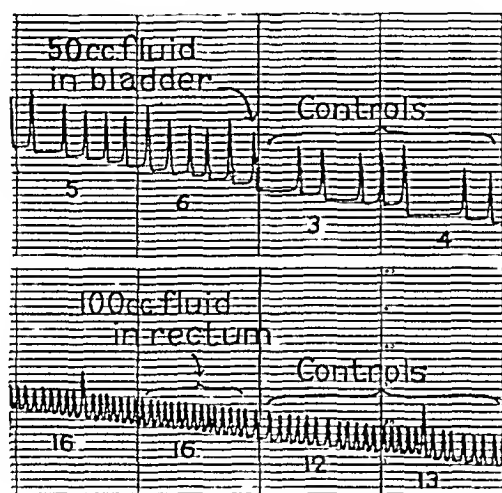


Fig. 6.—The distance between two adjacent vertical lines indicates one minute. The curves, which pass from right to left, represent spirometric tracings on a dog. In this animal a consistent but rather slight increase in respiration was produced either by distending the rectum with bismuth paste or by distending the bladder with saline solution. These effects have been found in the majority but not in all of the animals studied.

edema of the lungs in rabbits by compressing the left ventricle. However, one has to explain why it is that while the strain on the left side of the heart is constantly present in these patients, the onset of pulmonary edema occurs in sudden seizures. In this regard the suggestion of Fraser,⁵ that an increase in respiratory movements incident to the dyspneic seizure might lead to a further increase in pulmonary congestion, has seemed to merit study. According to this hypothesis the effect of an increase in ventilation would be to cause an increased venous return and hence a greater cardiac output. If because of overwork and disease the left ventricle were less able than the right to

7. Welch, W. H.: Virchows Arch. f. path. Anat. **77**:375, 1878

perform this added work, more blood would accumulate in the already congested lung. In an attempt to determine whether or not this hypothesis is correct further observations have been made.

1. Effect of Increased Respiratory Movements on the Cardiac Output: It is possible under certain conditions to determine qualitative changes in cardiac output by measuring the absorption of oxygen. Since the amount of oxygen consumed by the lungs themselves is so small as to be negligible, it is evident that all of the oxygen which is removed from the inspired air passes into the blood. Over any period of minutes or longer, the amount of oxygen passing into the venous blood in the lungs is equal to and determined by the amount of oxygen passing from the arterial blood in its transit through the tissue capillaries. However, any sudden increase in the amount of blood passing through the lungs must be immediately reflected by a similar increase in the amount of oxygen absorbed unless the amount of oxygen in the arterial blood is to undergo diminution. As this excess blood passes through the tissues, less oxygen will be removed, and the venous blood, returning richer in oxygen, will absorb less oxygen per unit of blood than before. Hence, even though the flow of blood through the lungs remains elevated, the intake of oxygen will tend to return to normal after recirculation has occurred, but before recirculation has taken place, changes in the absorption of oxygen will afford a measure of the changes in flow of blood through the lungs, i. e., of changes in the cardiac output.

The filling of the heart is dependent on the "effective venous pressure," i. e., on the difference between the pressure in the veins and that in the right auricle, which in turn is affected by the intrathoracic pressure. Under ordinary conditions one would expect an increase in ventilation to diminish the average pressure in the chest cavity (i. e., to make this pressure more negative), and hence, if other things remained equal, the degree of cardiac filling should be greater with a resultant increase in the cardiac output and in the pulmonary flow of blood, which would cause an increase in absorption of oxygen during the time required for one circulation of the blood to occur. That these events actually do take place in normal persons as a result of overventilation is indicated clearly by the fact that the consumption of oxygen is increased during the determinations of cardiac output by the Krogh-Lindhard, Grollman and similar methods, which necessitate an increase in the respiratory movements for periods of from fifteen to twenty seconds. There is some question, however, as to the ability of the cardiac output to increase in a person who has congestive heart failure. In order to test the matter the observations shown in table 2 were made. Under resting conditions the ventilation and consumption of oxygen were determined by means of a face mask, a Tissot spirometer and analysis with the

Haldane apparatus. The subject was then instructed to increase his ventilation, and the consumption of oxygen was determined during the first fifteen or twenty seconds of the overventilation and during subsequent periods. Any immediate rise in consumption of oxygen could be

TABLE 2.—*Immediate Effects of Overventilation on Intake of Oxygen*

Subject	Date	Conditions	Ventila- tion per Minute, Liters	Intake of Oxygen per Minute, Cc.	Excretion of Carbon Dioxide per Minute, Cc.	Respira- tory Quotient
Normal subject W. G. H.	3/18	Rest.....	4.52	180	146	0.81
		Maximal overventilation				
		1st 15 seconds.....	84.4	1,715	1,545	0.90
		2d 15 seconds.....	64.2	497	892	1.79
	3/24	Rest.....	5.23	166	180	1.08
		Maximal overventilation				
		1st 40 seconds.....	74.6	638	1,200	1.87
		40th to 60th second.....	37.0	497	826	1.66
	3/25	Rest.....	3.97	169	140	0.83
		Moderate overventilation				
		1st 20 seconds.....	33.5	436	686	1.57
		2d 20 seconds.....	29.4	299	632	1.59
		3d 20 seconds.....	29.0	293	476	1.63
	3/26	Rest.....	3.95	179	160	0.90
		Moderate overventilation				
		1st minute.....	22.2	512	634	1.24
		2d minute.....	20.6	278	497	1.68
	3/26	Rest.....	3.98	179	160	0.90
		Moderate overventilation				
		1st 2 minutes.....	20.4	402	539	1.34
		2d 2 minutes.....	18.1	300	432	1.44
Subject with car- diac failure W. C.	3/25	Rest.....	4.35	211	173	0.82
		Mild overventilation 1st 20 seconds.....	20.4	505	661	1.31
		Moderate overventilation (after intervening period of rest for 15 minutes)				
		1st 20 seconds.....	44.7	967	1,228	1.27
	3/22	Rest.....	5.10	201	178	0.89
		Maximal overventilation				
		1st 15 seconds.....	18.5	509	508	1.00
		2d 15 seconds.....	17.0	294	333	1.13
	3/23	Rest.....	5.43	192	165	0.86
		Maximal overventilation				
		1st 10 seconds.....	22.2	511	540	1.06
		10th to 30th second.....	25.0	403	448	1.11
Subject with car- diac failure P. F.	3/24	Rest.....	10.5	273	245	0.90
		Maximal overventilation				
		1st 20 seconds.....	33.1	544	611	1.12
		2d 20 seconds.....	32.0	322	421	1.31

due only to an augmented cardiac output, whereas, a delayed rise would be attributable to a true increase in tissue metabolism as a result of the greater muscular activity incident to the augmented respiratory movements.

Six observations were made on two normal subjects, and three tests were done on two patients with cardiac disease. The different experi-

ments varied in the intervals of time used and in the degree of over-ventilation employed. The various subjects showed somewhat different quantitative responses, but the qualitative effect of the overventilation was the same in all instances. Each time there was a striking immediate rise in the consumption of oxygen during overventilation. Later, although the increased breathing continued, consumption of oxygen declined markedly but remained well above the resting level as long as the increased ventilation was maintained. Regardless of the intervals of time employed, the absorption of oxygen always took place at a faster rate during the first than during the latter part of overventilation. The patients with cardiac failure who were not able to over-ventilate as much as were the normal subjects showed similar but less marked initial increases in absorption of oxygen. Furthermore, in a given subject on a given date there was a parallelism between the degrees of increase in consumption of oxygen and in ventilation (table 2, subject J. A. C., March 25, 1932).

These results seem to admit of only one interpretation, i. e., that increasing the ventilation causes an increase in cardiac output, not only in normal persons but in persons with cardiac failure.⁸

2. Effect of Increased Respiratory Movements on the Vital Capacity: The observations which have just been reported indicate that the amount of blood passing through the lungs is increased when the ventilation is increased. In a person with normal relationships of pressure in the lesser circulatory system one would not expect such a change to cause congestion of the lungs, but the result might be quite different in a patient in whom there existed an impediment to the escape of blood from the lungs because of "back pressure" from a dilated left ventricle. Direct measurements of the amount of blood in the lungs of patients are not possible, but the vital capacity constitutes a guide to qualitative alterations in the degree of pulmonary congestion. Consequently we have made comparisons of the vital capacity as determined immediately after normal breathing with that measured following one minute of moderate—not maximal—overventilation. In each subject from three to five such comparisons were made, the vital capacity being recorded graphically for the sake of accuracy in measurement.

Examples of the results are shown in figure 7. Normal subjects showed a definite tendency to have higher vital capacities following overventilation, a finding which is probably to be interpreted as indicating that the volume of blood in the lungs was somewhat diminished by the increased respiratory movements. In view of the

8. Since this paper was written our attention has been called to the study of Grollman (*Am. J. Physiol.* **94**:287, 1930), who observed an increase in the cardiac output of normal men during overventilation.

spongelike structure of the lungs such a result is not surprising. Patients with cardiac failure usually—but not always—exhibited some slight diminution in vital capacity following overventilation. This effect, which was the reverse of that observed in normal persons, apparently indicates that when there is obstruction to the outflow of blood from the lungs (left ventricular failure) an increase in the venous return will tend to cause greater pulmonary congestion.

It appears, therefore, that the increased ventilation produced by any of the causes which have been mentioned may in itself become a further cause of pulmonary congestion and hence initiate a vicious cycle. It is true that the decrease in vital capacity which occurred in our patients as a result of overventilation was of slight degree, being usually not more than 100 cc. However, in one patient voluntary over-

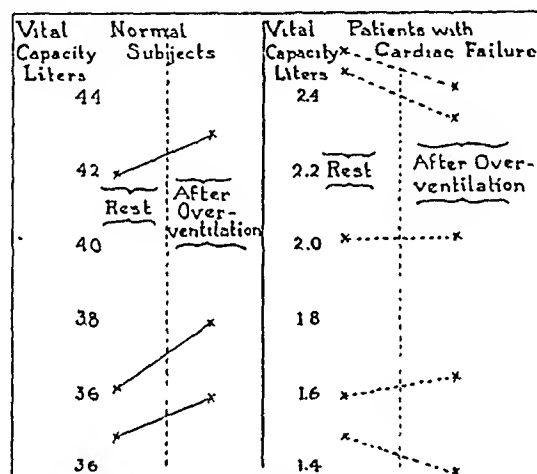


Fig. 7.—Each point represents an average value for from three to five measurements of vital capacity. In the normal subjects voluntary overventilation for one minute was followed by a slight increase in this function. The patients with cardiac disease showed no constant effect, although the vital capacity was slightly lower in three of the five subjects. It is possible that the other two persons would have reacted similarly, had the overventilation been maintained for a longer time. In a sixth patient acute edema of the lungs developed following voluntary overventilation. During the attack the vital capacity apparently decreased about 25 per cent, but since the accuracy of this measurement is questionable the values for this patient were not included in the figure.

ventilation produced a typical seizure of cardiac asthma which was accompanied by acute pulmonary edema and was so severe as to render accurate measurements of vital capacity impossible.

This patient, a Negress, aged 49, with cardiac failure secondary to hypertension, was having frequent attacks of paroxysmal dyspnea which awakened her from sleep and which always followed coughing. At a time when she was free from dyspnea, observations were made concerning the effect of overventilation on her vital capacity. Following voluntary increase in respiratory movements for one-half minute, she began to cough and was short of breath for several minutes

thereafter. A quarter of an hour later she was quite comfortable again, and the procedure was repeated with similar results. Following a third period of voluntary overventilation for one minute she became excessively dyspneic, had to sit upright and hang her legs over the bed; she coughed violently, broke out into profuse perspiration, began to tremble, developed muscular twitchings and expectorated frothy sputum. The vital capacity measured at this time was about 25 per cent less than it had been when measured following quiet breathing a few minutes before. (No tracing from this patient was included in figure 7 because the accuracy of the value obtained under such conditions was considered questionable.) During the seizure of dyspnea moist râles, which had not been present previously, could be heard over the bases of both lungs. For several minutes the patient presented all the signs of a severe attack of pulmonary edema. The administration of morphine was followed by relief within a short time.

Furthermore, in a previous paper⁹ it was shown that in a dog the respiratory rate may be markedly affected by the introduction of as little as 25 cc. of blood into the lungs, and hence it was concluded that a barely measurable decrease in vital capacity might, if produced by pulmonary congestion, cause pronounced respiratory stimulation. This in turn would lead to further congestion, and so on. The administration of morphine would tend to break the vicious cycle because of the diminished respiration with the resulting decreased inflow of blood into the lungs and diminished pulmonary congestion (table 1). Fraser⁵ believed that this was the mechanism whereby morphine produced improvement in patients with cardiac asthma, and our data are in support of this suggestion.

In many patients the attacks of dyspnea subside spontaneously without morphine or other sedatives. The expectoration of mucus and the consequent relief of cough have apparently been responsible for the spontaneous termination of the attack in a number of patients. Likewise, the milder cases have frequently been relieved by the assumption of a more nearly upright posture, in which the vital capacity is greater. In other instances, urination, belching or bowel movements have produced relief by abolishing the precipitating cause of the attack. Possibly the depressant effect on respiration of loss of carbon dioxide from overventilation may predominate in some patients over the reflex respiratory stimulation due to the pulmonary congestion. Concerning this point we have no data, as our patients have received morphine whenever the attack was severe and not relieved in a short time by one of the procedures already mentioned. On the other hand, if the latter factor predominates, the lungs, which were congested before the onset of the attack, should become progressively more engorged during the seizure. Because of their loose structure it is

9. Harrison, W. G., Jr.; Calhoun, J. A.; Marsh, J. P., and Harrison, T. R.: Congestive Heart Failure: XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, *Arch. Int. Med.* **53**:724 (May) 1934.

probable that a great quantity of blood may accumulate in the lungs without causing marked rise in the pulmonary capillary pressure. Eventually, however, as the congestion becomes more severe, this pressure will rise, at first slowly and then more rapidly. Once the limits of elasticity are approached, the further addition of a small amount of blood will cause a marked rise in pressure (fig. 8). Such a series of events will, if unchecked, result in edema of the alveolar spaces when the pulmonary capillary pressure has risen above the counteracting osmotic pressure of the plasma protein.¹⁰

3. Effects of Edema of the Lungs on the Respiration and on the Circulation: Clinical experience indicates that when acute pulmonary edema develops in a patient with cardiac asthma the situation becomes extremely serious and may go on to a fatal issue unless proper therapeutic measures are immediately instituted. The reasons for this

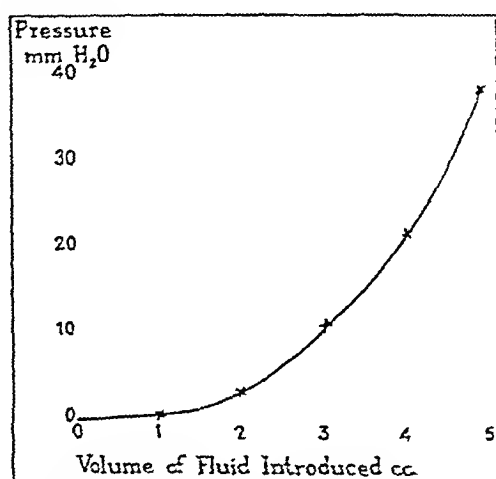


Fig. 8.—This curve illustrates the relations of volume to pressure in a strip of vena cava of a dog. The tributary branches having been ligated, a small cannula was introduced at one end of the vein, and the other end was then ligated. Water was now introduced, 1 cc. at a time, and the pressure was observed. It is seen that the pressure increased very little at first and then rapidly. This result, which is similar to those found by other investigators, is dependent on the fact that the vein is collapsible and easily distensible until it is fairly well filled, but after this point is reached the walls are resistant, and hence any further increase in volume is accompanied by a disproportionately large increment in pressure.

are not far to seek. In the first place, the mere presence of a large amount of fluid in the lower respiratory tract tends to cause violent coughing, and we have shown that cough is a potent cause of dyspnea in

10. The observations which have just been mentioned may afford an explanation of the fact that patients with severe Cheyne-Stokes respiration, although having severe pulmonary congestion, are not likely to have attacks of acute pulmonary edema. Their lungs might become more congested during hyperpnea, but the engorgement would be likely to diminish during apnea, and this would probably tend to prevent the congestion from progressing to the point of producing sudden and severe edema of the lungs.

patients with cardiac failure. Furthermore, in experiments on dogs it was shown¹¹ that the introduction of fluid into the lungs via the trachea caused marked acceleration of breathing, even though the cough had been abolished by anesthesia. When small amounts of fluid were used, the augmented breathing was evidently a reflex effect, as the respirations were not accelerated if the vagus nerves had been cut previously. When larger amounts of fluid were introduced, there was the additional factor of respiratory stimulation dependent on inadequate aeration of the blood with anoxemia and, in some instances, retention of carbon dioxide. Unless it is assumed that the respiratory physiology of man is radically different from that of the dog, it seems likely that pulmonary edema in man causes stimulation (both reflex and chemical) of the breathing, with a resultant increase in venous inflow, which would tend to cause more congestion and edema and thus to intensify the vicious cycle.

There is another important effect of pulmonary edema, quite aside from its direct influence on respiratory movements. That edema of the lungs may cause severe lack of oxygen in the arterial blood is well known (Eppinger, von Papp and Schwarz; Fraser; subject W. L., table 1 of this paper). It was shown by Harrison and Blalock¹² that arterial anoxemia produced by rebreathing caused marked increase in the cardiac output of dogs. Grollman¹³ has recently confirmed their observations by finding that the cardiac output of human subjects was greater at Pike's Peak than at lower altitudes.

Jones¹⁴ studied in this laboratory the effect of "pulmonary edema" (caused by introducing saline solution into the trachea) on the cardiac output of dogs. A summary of his findings is shown in table 3, and it can be seen that of the ten animals studied, eight had an increase in cardiac output after receiving saline solution intratracheally. The degree of increase varied markedly, however, in the different dogs. In one animal no change was noted, and the tenth dog had a diminished cardiac output. The cause of these atypical results in two experiments is still under investigation.

Cause of the Occurrence of Asthmatic Râles in Persons with Cardiac Asthma.—It is well known that in some patients musical and sonorous râles develop during severe attacks of cardiac asthma and more especially if there is an associated acute pulmonary edema. These

11. Harrison, T. R.; Calhoun, J. A.; Cullen, G. R.; Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure: Reflex Versus Chemical Factors in Production of Rapid Breathing, *J. Clin. Investigation* **11**:133 (Jan.) 1932.

12. Harrison, T. R., and Blalock, A.: Regulation of Circulation; Effects of Severe Anoxemia of Short Duration on Cardiac Output of Morphinated Dogs and Trained Unnarcotized Dogs, *Am. Physiol.* **80**:169 (March) 1927.

13. Grollman, 9.: Physiological Variations of Cardiac Output of Man, *Am. J. Physiol.* **93**:19 (May) 1930.

14. Jones, E.: Personal communication to the authors.

auscultatory phenomena may be so like those of bronchial asthma as to lead to a mistake in diagnosis if the patient is hurriedly examined. No satisfactory explanation has, to our knowledge, yet been advanced as to the pathogenesis of these physical signs in patients with cardiac asthma. Since attacks of bronchial asthma are usually assumed to be due to active bronchoconstriction, it occurred to us that possibly fluid in the alveoli might have a reflex bronchomotor action. In order to test this hypothesis, experiments were performed on dogs, but we were unable to demonstrate any such effect. (Such negative results are necessarily inconclusive and may have been due to the fact that the method used was not sufficiently delicate to detect small changes in bronchial caliber). Acute edema of the bronchial walls was thought of as another

TABLE 3.—*Effect of Introducing Fluid into the Trachea on the Cardiac Output of Dogs*

Date	Experiment	Control Studies		Results After Introducing Saline Solution into the Trachea	
		Arterial Oxygen Saturation, per Cent*	Cardiac Output per Minute, Liters	Arterial Oxygen Saturation, per Cent	Cardiac Output per Minute, Liters
12/ 6.....	1	91	1.17	47	3.13
12/13.....	2	91	2.84	67	2.85
12/17.....	3	99	2.83	75	3.23
12/20.....	4	90	1.77	57	2.23
3/11.....	5	84	2.49	54	3.20
3/18.....	6	95	0.68	69	1.60
4/ 2.....	7	86	1.40	78	1.74
4/ 9.....	8	93	1.34	83	1.57
4/17.....	9	95	1.51	46	1.13
4/19.....	10	85	2.86	28	8.27 (?)

* The low arterial saturation present during the control studies is to be attributed to the morphine which was given to the animals in order to keep them quiet during the observations.

possible cause of the auscultatory phenomena under discussion. In order to determine whether or not this occurred, a study was made of pathologic material already at hand.

The lungs from twenty-seven patients were studied. Of these, ten died with cardiac failure; the remaining seventeen were chosen at random. Notes were made in relation to the occurrence of pulmonary edema, bronchial edema, active congestion, passive congestion, pneumonia and miscellaneous complicating factors.

The diagnosis of bronchial edema was made when precipitated material was observed beneath the elevated mucosa. It was realized that elevation or desquamation of the mucosa could occur as an artefact of sectioning or fixation, and therefore the diagnosis of bronchial edema was not made unless this change was accompanied by precipitation of serum beneath the mucosa.

From these cases it seems that we have to differentiate two types of edema, the one associated with a noninflammatory edema of the lungs, the other associated with an acute inflammatory process of the

lungs and bronchi. In the former the wall of the bronchus is entirely free from inflammatory exudate; in the latter it is heavily infiltrated with polymorphonuclear leukocytes.

These two types of edema are illustrated by the photographs in figure 9. The upper photograph illustrates the type of edema which is associated with the acute inflammatory process within and around

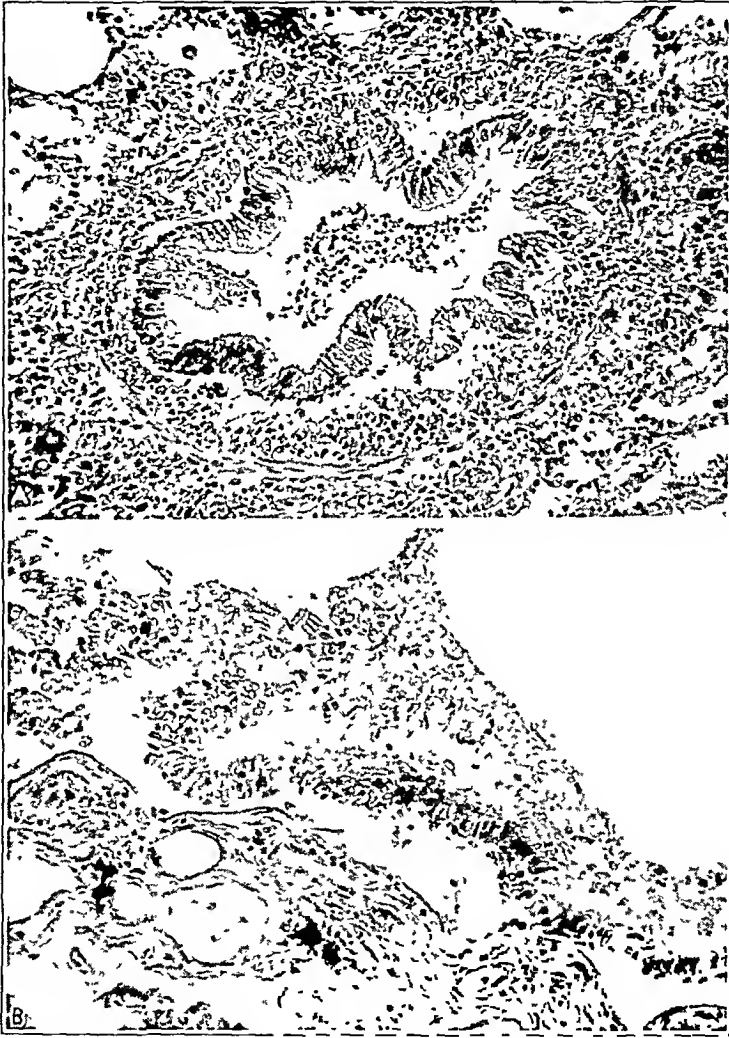


Fig. 9.—Types of bronchial edema. *A*, with acute inflammatory process; *B*, without inflammatory exudate.

the bronchi. The wall is infiltrated with lymphocytes and polymorphonuclear leukocytes, and the fibers are stretched apart. The mucosa is elevated, and there is a collection of precipitated serum beneath it. In the lower photograph the picture is entirely different. The bronchial wall is thin and free from inflammatory exudate. The surrounding alveoli contain precipitated serum but no leukocytes. The mucosa is elevated, and beneath it there is precipitated serum. The desquamation of the epithelium is interpreted as an artefact.

COMMENT

The data which have been reported tend to support the hypothesis that the fundamental underlying cause of cardiac asthma is congestion of the lungs dependent on "back pressure" from dilatation of the left side of the heart. The mechanism is thus quite different from the attacks of coughing and dyspnea experienced by patients with cardiac failure secondary to chronic pulmonary disease (cor pulmonale). The

TABLE 4.—*Various Types of Nocturnal Dyspnea*

Condition	Characteristic Clinical Features	Underlying Cause	Precipitating Causes	Comment
Orthopnea	Dyspnea partially or entirely relieved by sitting up		Assumption of recumbent posture, causing further congestion of lungs	May occur alone; nearly always present in patients with other types of nocturnal dyspnea
Evening dyspnea	Not paroxysmal; absent or mild on first awakening in the morning; develops gradually during the day; worse in the evening; may prevent patient from going to sleep; does not occur during sleep	Dilatation of left side of heart (from overwork or disease) leading to back pressure and congestion of lungs with consequent decrease in respiratory reserve because of (a) decreased vital capacity and (b) reflex stimulation of respiration	Increased degree of pulmonary congestion in evening as compared to morning, because of greater bodily activity when awake than when asleep	Patients may also have cardiac asthma or Cheyne-Stokes respiration
Cheyne-Stokes respiration	Repeated short paroxysms of dyspnea (hyperpnea) separated by intervals free from dyspnea (apnea), appearing only or in exaggerated form at onset of sleep		Sudden decrease in sensitivity of respiratory center at onset of sleep, causing apnea; increased sensitivity of respiratory center on awakening, causing hyperpnea and dyspnea	Other types of nocturnal dyspnea may also be present
Cardiac asthma	Paroxysms of dyspnea occurring after patient has been asleep for some time; often associated with "asthmatic rales"; likely to lead to acute pulmonary edema		Most frequently, cough; also nightmares, desire for urination, abdominal distention, constipation, hunger, warmth, etc.; on awakening, sudden increase in sensitivity of respiratory center leads to increased respiratory movements which cause additional congestion of lungs	Other types of nocturnal dyspnea may also be present

dyspnea in such patients is primarily of pulmonary origin. Because the primary strain is on the right rather than on the left ventricle congestion and edema of the lungs do not occur.

When the observations in the present article are considered in relation to those in the three preceding ones it is possible to make a classification of the various types of nocturnal dyspnea. Such a classification is shown in table 4. It can be seen that nocturnal dyspnea may be of gradual onset (evening dyspnea) or paroxysmal. It may occur either before (evening dyspnea), during (Cheyne-Stokes respiration) or after (cardiac asthma) the onset of sleep. Regardless of the type of dyspnea, the factor of posture is nearly always an important one, and orthopnea

is nearly always present as an additional type of dyspnea. Furthermore, patients with either cardiac asthma or Cheyne-Stokes respiration frequently have evening dyspnea. And finally, all four types of nocturnal dyspnea may occur in the same patient during the same attack of congestive heart failure.

In this series of articles we have emphasized the importance of nocturnal dyspnea. However, the observations are equally applicable to resting dyspnea in general in patients with cardiac disease. A patient who has sufficiently severe pulmonary congestion may paradoxically have any of the various types of nocturnal dyspnea during the day and while awake. In such instances the underlying cause is so severe that the various precipitating factors which have been discussed are unnecessary. Even then, however, the precipitating factors still play a rôle, for no matter how severe the discomfort may be in the morning on awakening, it will usually be worse after the patient has been awake for a number of hours, and unless prevented by proper therapeutic measures paroxysmal exacerbations of the dyspnea will usually occur during or after the onset of sleep. The final result in untreated patients is the agonizing continuous dyspnea which is severe at all times and still worse at some times, which renders sleeping impossible and eating impracticable, which exhausts the patient and produces cardiac cachexia, and which persists until an infarction, a final attack of pulmonary edema or a merciful bronchopneumonia ends the story.

SUMMARY

1. Cardiac asthma has been defined and has been differentiated from other types of paroxysmal and of nocturnal dyspnea occurring in patients with cardiac disease.

2. The dyspnea of cardiac asthma is not usually associated with abnormalities in the oxygen, carbon dioxide or hydrogen ion content of the arterial blood.

3. Relief of the seizure by morphine is not associated with constant alteration in the gases of the blood, but is followed by a decrease in ventilation and is usually accompanied by an increase in vital capacity.

4. Pulmonary congestion, with its twofold effect of decrease in vital capacity and reflex respiratory stimulation, is always present and appears to be the underlying cause of cardiac asthma.

5. There are a number of different precipitating causes of the seizures. Of these, cough is the most common. Less frequently, fear—produced by unpleasant dreams—abdominal distention or warmth may precipitate the seizures.

6. Each of these precipitating factors appears to act by increasing the ventilation.

7. It has been shown that, both in normal persons and in patients with cardiac disease, an increase in ventilation is accompanied by a rise in consumption of oxygen, which occurs immediately and thereby indicates that the cardiac output is also increased.

8. The effects of voluntary overventilation on the vital capacity were studied in normal subjects and in patients with left ventricular failure. The former persons usually had a slight rise in vital capacity, but the reverse effect was usually obtained in the patients.

9. A typical seizure of cardiac asthma was produced in one patient by voluntary overventilation and in another subject by voluntary coughing.

10. Acute pulmonary edema causes both chemical and reflex stimulation of breathing and may thus accentuate dyspnea. It has also been shown that in dogs "edema" of the lungs produced by introducing Ringer's solution may cause marked anoxemia with a consequent increase in the cardiac output.

11. It has been shown that patients dying with congestion of the lungs may have a noninflammatory edema of the bronchial walls, and this is believed to be responsible for the musical and sonorous râles which are often heard during the dyspneic seizures. Thus, an "obstructive" dyspnea may be superimposed on a "reflex" dyspnea.

12. The occurrence of the attacks during sleep appears to be dependent on the depressed irritability which allows the various stimuli mentioned to become excessive before they awaken the patient. On awakening there is marked increase in breathing because of the sudden increase in irritability of the respiratory center, plus the strong stimulus. The resulting increase in ventilation tends to cause additional pulmonary congestion, which leads to further increase in ventilation. The vicious cycle so started may progress to acute pulmonary edema unless it is broken by the patient's assuming the upright posture, by the administration of morphine or by removal of the precipitating cause, i. e., expectoration of mucus, relief from fear of nightmares, etc.

13. The same factors which cause cardiac asthma by night may cause seizures during the day and result in more or less continuous dyspnea.

14. Four types of nocturnal dyspnea occur in patients with cardiac disease; these are orthopnea, evening dyspnea, Cheyne-Stokes respiration and cardiac asthma. They all have a common underlying cause, namely, pulmonary congestion consequent to "back pressure" from the left side of the heart.

Dr. James Dawson, of the Department of Pathology, Vanderbilt University, assisted in the interpretation of changes observed in the bronchial mucosa, and Dr. Edgar Jones permitted us to publish his data concerning the effect of edema of the lungs on the cardiac output.

PERIOSTEAL OSSIFICATION IN MYELOGENOUS LEUKEMIA

REPORT OF A CASE ASSOCIATED WITH ACUTE RHEUMATIC FEVER

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The occurrence of pain in the joints and bones in the course of leukemia, of both the lymphatic and the myeloid type, has been recognized by clinicians for many years (Naegeli,¹ Poynton and his co-workers² and Smith³). These manifestations have consisted of not only pain and tenderness in the long bones, but also swelling, tenderness and redness in the joints clinically indistinguishable from that which occurs in acute rheumatic fever. These findings usually receive their correct interpretation on the basis of the existence of the hematologic and physical features of leukemia, and little diagnostic difficulty is encountered. Several cases in the aleukemic and acute states, in which the existence of leukemia was less obvious because of the absence of changes in the circulating blood and clinically demonstrable involvement of the liver, spleen and lymph nodes, have presented diagnostic problems in which, particularly, the differentiation from acute rheumatic fever was difficult (Taylor,⁴ Karelitz,⁵ Seward,⁶ Poynton and his co-workers² Smith³ and Cooke⁷).

From the Department of Laboratories and Pediatric Service, Lebanon Hospital.

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2. Poynton, F. J., and Lightwood, R.: Lymphatic Leukemia with Infiltration of the Periosteum Simulating Acute Rheumatism, *Lancet* **1**:1192 (June 4) 1932. Poynton, F. J., and Moncrieff, A.: Subcutaneous Nodules in the Scalp in Fatal Cases of Glandular Enlargement with Mononucleosis, *ibid.* **2**:812 (Oct. 19) 1929. Poynton, F. J.; Thursfield, H., and Paterson, D.: The Severe Blood Diseases of Childhood, *Brit. J. Child. Dis.* **19**:128, 1922.

3. Smith, C. H.: Leukopenic Myeloid Leukemia Associated with Arthritis, *Am. J. Dis. Child.* **45**:123 (Jan.) 1933.

4. Taylor, H. K.: Periosteal Changes in Lymphatic Leukemia, *Radiology* **6**:523, 1926.

5. Karelitz, S.: Unusual Forms of Periosteal Elevation, *Am. J. Dis. Child.* **33**:394 (March) 1927.

6. Seward, B. P.: Lymphatic Leukemia with Severe Pains in the Joints, *M. J. & Rec.* **131**:444 (May 7) 1930.

7. Cooke, J. V.: Acute Leukemia in Children, *J. A. M. A.* **101**:432 (Aug. 5) 1933.

Several reported cases contain descriptions of morphologic changes responsible for the skeletal symptoms, but the postmortem examination in many other cases revealed no underlying anatomic basis. The reported anatomic changes, in most instances, refer to osteoporotic and osteosclerotic alterations in the long bones, and, in a few cases, to subperiosteal infiltrations (see Comment).

We have been unable to find a comprehensive description of the exact character of the periosteal changes, which they appear to merit because of their not infrequent discovery in roentgen studies (Geschickter and Copeland⁸). It would appear at first that an infiltration of this type, like, indeed, any other infiltration in the course of leukemia, is of no unusual interest. But the fact that leukemia is not usually considered in the differential diagnosis of periosteal elevation, and that this may exist in aleukemic and acute phases, in which the diagnosis of leukemia is otherwise impossible, merits some focus of attention on this phenomenon.

Our case affords an excellent opportunity for this, as well as for recording a unique instance in which postmortem examination demonstrated the actual coexistence of acute myeloid leukemia and acute rheumatic fever, no similar case having been found in the literature.

REPORT OF CASE

History.—S. A., a girl, white, aged 11½, was first admitted to Lebanon Hospital on Aug. 24, 1932, to the surgical service of Dr. L. M. Kahn. In the past, the patient had had two or three attacks of tonsillitis and had been subject to occasional colds and sore throats. A mastoidectomy had been performed at the age of 16 months. The onset of the menses occurred at the age of 10½, and the patient menstruated regularly every twenty-eight days, for six days. The bleeding was never excessive. The last period occurred in August, and the patient had an amenorrhea until the time of death in November.

On admission, she complained of having had attacks of pain in the lower half of the left arm since June, 1932. On examination a definite fusiform swelling of the lower half of the left humerus, with tenderness on pressure, was found. The temperature ranged between 98.6 and 100.5 F. Examination of the blood showed the following: hemoglobin, 80 per cent; red cells, 4,000,000; white cells, 16,400; polymorphonuclears, 82 per cent, and lymphocytes, 18 per cent. The picture was essentially that of an infection, and a tentative clinical diagnosis of subacute osteomyelitis was entertained. However, roentgen examination of the left elbow disclosed a marked thickening of the periosteum on all sides of the left humerus in its lower half. The cortex and medulla showed no abnormality (fig. 1). The Wassermann reaction was negative, and the Wassermann examination of the parents' blood done several months later was also negative. A diagnosis of chronic

8. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931, p. 617.

periostitis of unknown origin was made, and the patient was discharged on September 1, one week after admission, unimproved.

After returning home the patient continued to complain of pain in the left elbow, and in the right ankle and knee as well. About two weeks after her discharge tonsillectomy was performed, five carious teeth being extracted at the same time. These procedures were not followed by any unusual degree of hemorrhage. The patient was apparently well for the next week; then she began to complain of pain in the right wrist, and then in the left wrist and in the toes of both feet. The

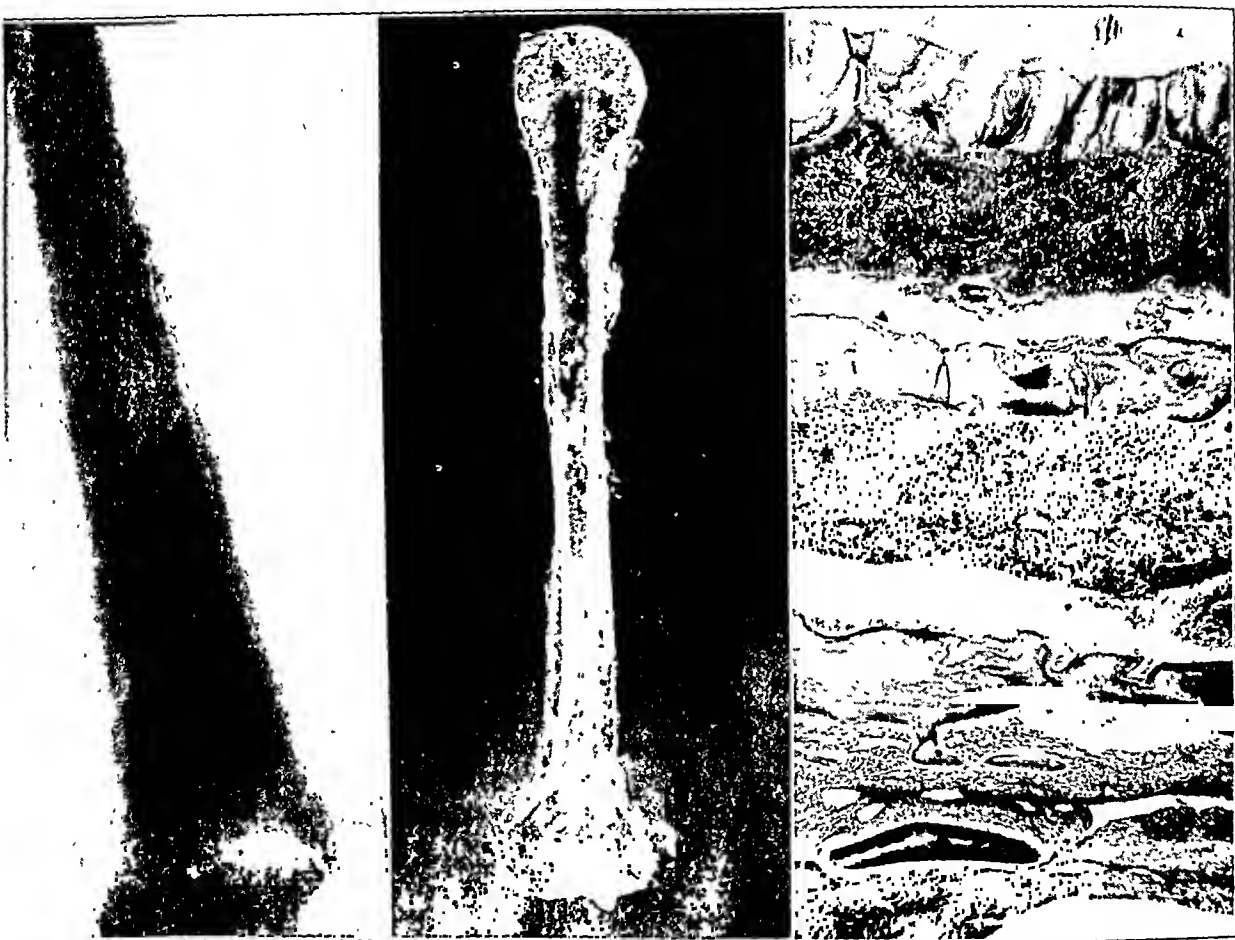


Fig. 1.—The roentgenogram on the left, taken on Aug. 25, 1932, shows periosteal elevation and thickening at the lower end of the left humerus. The center photograph is a cross-section of the left humerus and shows periosteal elevation and thickening and subperiosteal infiltration. The marrow is leukemic. The photomicrograph on the right shows the histologic appearance of the elevated, thickened periosteum at the lower end of the left humerus. The shaft of bone is below, out of the picture. Newly formed bony lamellae with intervening layers of leukemic infiltrate are seen.

temperature rose and became septic, and a week after the onset of these symptoms, on October 6, the patient was readmitted to the pediatric service of Dr. Charles Herrman.

Examination and Course.—On examination, the child appeared acutely ill. There were slight swelling, tenderness and limitation of motion of the left wrist. The

left elbow showed the same findings as on previous examination, but there was no tenderness. The small joints of the fingers and toes were tender but not swollen. The heart showed no abnormalities, except for tachycardia. The liver, spleen and lymph nodes were not palpable. There was also a purplish, more or less generalized, scarlatiniform erythema, especially marked on the abdomen and chest. This was considered by Dr. L. Chargin, the attending dermatologist, to be due to the administration of salicylates, and later when amidopyrin was substituted, the rash disappeared. The temperature on admission was 102 F., and the pulse rate, 130. The blood count showed the following: hemoglobin, 55 per cent; red cells, 3,610,000; white cells, 20,000; polymorphonuclears, 72 per cent; lymphocytes, 26 per cent, and monocytes, 2 per cent. The administration of salicylates and amidopyrin produced a marked remission in fever and pain in the joints.

Data on Blood Studies

	8/24	10/6	10/18	10/29	11/5	11/11	11/16
Hemoglobin.....	80%	55%	52%	51%	46%	35%	28%
Red blood cells.....	4,000,000	3,610,000	3,520,000	3,610,000	2,910,000	1,920,000	1,760,000
White blood cells...	16,400	20,000	37,200	56,800	89,200	163,000	184,000
Neutrophils.....	82%	72%	78%	73%	30%	20%	15%
Lymphocytes.....	18%	26%	17%	17%	26%	8%	7%
Monocytes.....	2%	3%	1%	3%	1%	...
Eosinophils.....	2%	1%
Myelocytes							
Neutrophile.....	6%	46%	20%
Eosinophile.....	4%	27%
Myeloblasts.....	3%	8%	24%	58%
Normoblasts.....	1%	...	1%
Platelet count.....	120,000	...	70,000
Reticuloocytes.....	3%	...	1%
Bleeding time.....	4 min.
Congulation time..	5½ min.

On October 11, five weeks prior to death, the blood count was essentially the same as previously, the leukocytes numbering 18,300. Examination of the heart showed no clinical evidence of involvement, but two weeks later a systolic murmur was heard over the fourth intercostal space to the left of the sternum, and the second aortic sound was accentuated. An electrocardiographic tracing revealed myocardial damage, as evidenced by slurring of the QRS complex in all leads, and two premature auricular contractions in lead I. There was also absence of sinus arrhythmia, but no increase in the PR interval.

On October 18, four weeks prior to death, a routine blood count gave the first evidence of irregularity in the blood picture. The leukocytes numbered 37,200; the differential count was not significantly changed. The temperature at this time was normal.

On October 22, three weeks before death, the liver was first felt two finger-breadths below the costal margin. On October 24, the spleen was palpated for the first time just under the costal margin, and small lymph nodes were felt in the neck, axillae and groins. On October 25, after a tourniquet was applied to the arm in order to obtain a specimen of blood, it was noticed that many petechial hemorrhagic spots developed below the site of the tourniquet.

From this time on, progressive increase in size of the palpable lymph glands and spleen could be followed. The glands became moderately enlarged; the liver grew daily in size, and after two weeks extended to the umbilicus; at death, it almost filled the abdomen. The spleen did not appear to grow as rapidly, but roentgen examination showed it to be considerably enlarged.

On November 7, a few petechial hemorrhages were noticed on the face. These rapidly became more numerous and widespread, involving mostly the face, palate, chest and abdomen. Many hemorrhages were seen in the ocular fundi. One of these with a pale center was considered typical of leukemia by Dr. J. Ziporkes, the attending ophthalmologist.

Repeated examinations of the blood showed an advancing anemia and a progressive increase in the number of leukocytes with a differential count indicative of the presence of a myelogenous leukemia (Dr. H. Frosch, hematologist). At the time of death, the leukocyte count was 184,000. The cells were mainly of the myeloid series. At the beginning, immature polymorphonuclear cells predominated, with occasional myeloblasts and myelocytes. There was a gradual increase in the number of myeloblasts, which rose from 3 per cent, until at the time of death they constituted 58 per cent of the total number of cells. The platelet count was 120,000 per cubic millimeter; the reticulocytes, 3 per cent. Bleeding and coagulation time were within normal limits. The blood chemistry was normal. Repeated cultures of the blood were sterile.

Roentgenographic examination of the bones revealed a moderate degree of decalcification of all the bones of the upper extremities; small areas of bone absorption along the outer aspects of both scaphoid bones and in the lower end of the shaft of the left ulna, and periosteal thickening along the left humerus, as observed previously, and in the right ulna as well.

On November 11, a biopsy of a right inguinal lymph node was performed and was reported as showing "marked extramedullary myelopoiesis as seen in leukemic myelosis."

On November 12, 250 cc. of citrated blood was given by transfusion. Following the transfusion, the patient became much worse. She was drowsy and irritable, uttered loud cries and appeared to be very sensitive to touch. She became dyspneic, and complained of abdominal pain and inability to breathe, and died on November 16, six weeks after the second admission and five months after the onset of the symptoms.

Biopsy.—The capsule of the inguinal lymph node was thin, and for the most part, not infiltrated. A few foci of infiltration, however, were seen in the pericapsular fat tissue. The original lymphatic structure was recognizable in a few areas. The remainder of the node consisted of a diffuse arrangement of pale, large, young cells. With the oil immersion lens, the finer details of these cells appeared as follows: Scattered, isolated cells and solid nests of cells corresponded to the most primitive, undifferentiated, mesenchymal type. They were large and stellate, with processes. The cytoplasm did not stain. The nucleus was oval and free from nucleoli. A later stage of differentiation was seen in cells which were partially rounded. They possessed a basophilic cytoplasm, sometimes heavily granulated, a darker nuclear membrane, and one or two large, usually dark-staining nucleoli. A still later stage was recognized in completely rounded cells, somewhat smaller than the previously described type. These contained cytoplasmic granules, frequently eosinophilic, and a single round nucleus, possessing a sharp membrane and

multiple dark nucleoli. Many mitoses were encountered, as well as some mature polymorphonuclear cells. The blood vessels and lymphatics contained numerous immature granulocytes. An occasional plasma cell was seen (fig. 2).

The diagnosis was "marked extramedullary myelopoiesis as seen in leukemic myelosis."

Autopsy.—Gross changes: The gross appearance is shown in figure 3.

There was no jaundice, but there was a slight pitting edema over the anterior tibial regions, and numerous petechial hemorrhagic flecks were seen over the face, neck and arms. Similar flecks were seen in the conjunctivae and mucous membranes of the mouth. There was a scar in the right inguinal region where a biopsy specimen had been obtained previously. No rheumatic subcutaneous nodules were found.

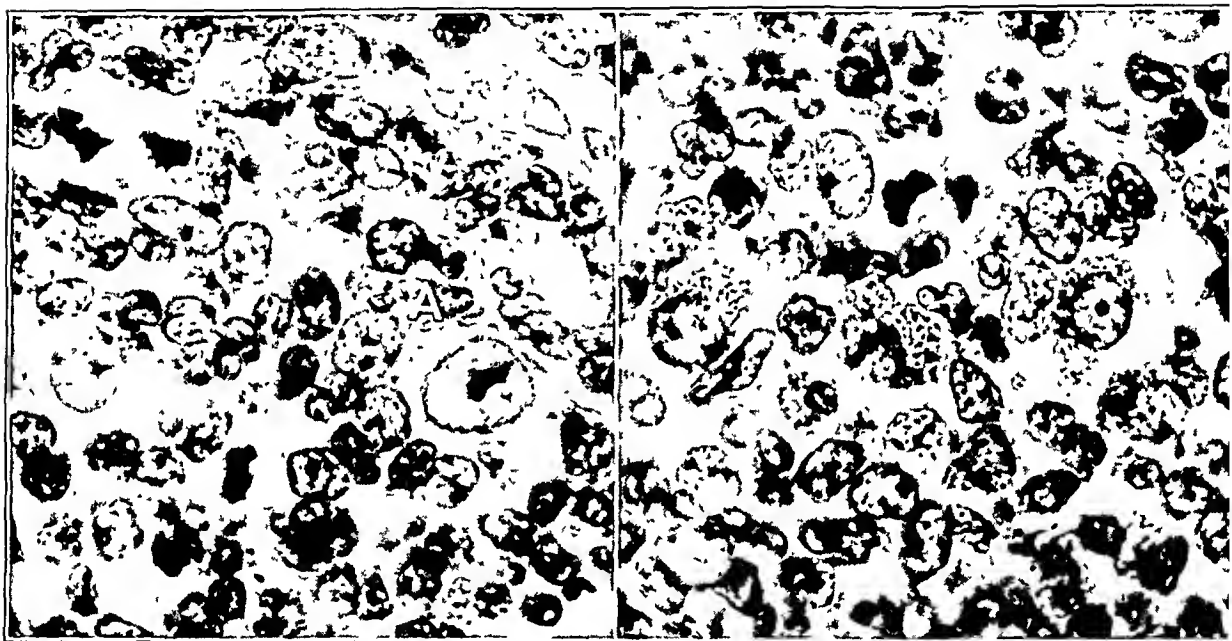


Fig. 2.—Photomicrographs of lymph node secured for biopsy. On the left is shown diffuse reticulum cell proliferation, with numerous mitoses. *A* indicates early differentiation into hemocytoblast. On the right are shown granules in cytoplasm of fixed mesenchymal cells undergoing hemocytoblastic differentiation.

The liver extended to the iliac crest on the right side and diagonally across the umbilicus to the hilus of the spleen. Hemorrhagic flecks were seen in the mesentery and serosal surfaces of the bowel.

All the lobes of the lungs had a distinctly nodular, firm consistency. A few scattered pleural petechiae were noted. On section, the lung, which cut with increased resistance, presented diffuse, confluent, raised, dry, granular hemorrhagic areas. The trachea and bronchi contained some purulent exudate, and their mucous membrane was markedly congested.

The pericardial cavity did not contain an increased quantity of fluid or adhesions. All four chambers of the heart were moderately dilated, but there was no distinct hypertrophy. The epicardium and endocardium contained scattered small hemorrhagic flecks. The foramen ovale was closed. The tricuspid, pulmonic and aortic valves presented no abnormalities. The cusps of the mitral valve were diffusely thickened, and, along the entire closing margin, a row of small, firm, pale vegeta-

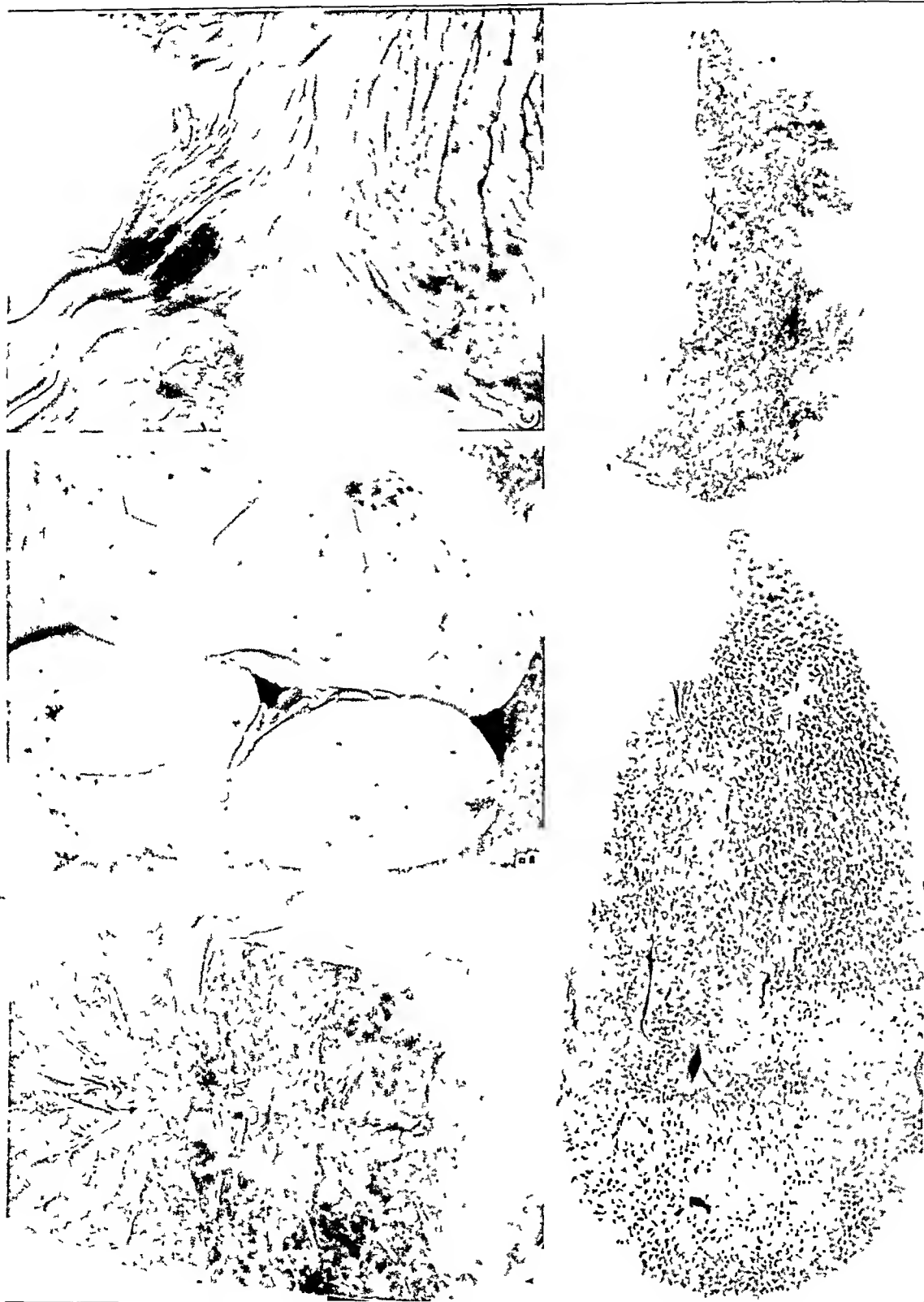


Fig. 3—Gross appearance of organs at autopsy. *A*, the lungs showing confluent bronchopneumonia; *B*, the kidneys showing diffuse pallor and focal hemorrhagic infiltrations; *C*, the esophagus showing hemorrhagic leukemic plaques and shallow ulcers, with petechial hemorrhages of the gastric mucosa; *D*, the liver showing diffuse periportal infiltrations, and *E*, the spleen showing diffuse infiltrations and infarcts.

tions was present. The blood vessels were not grossly visible in these cusps. The chordae tendineae were not thickened or adherent, and their insertion was normal. The left auricular endocardium was smooth. The coronary arteries were normal. The aorta was of normal caliber and elasticity. The myocardium was reddish brown, and presented scattered hemorrhagic and grayish streaks.

The thymus appeared hyperplastic.

The liver weighed 2,500 Gm. The capsule was a grayish yellow and pale, and the parenchyma shining through had a cobbled appearance. On section, the surface consisted of an anastomosing network of broad gray-white channels. No nodular infiltrations were seen. The gallbladder and bile ducts were normal.

The peripancreatic lymph nodes were enlarged, and at one point there appeared to be a nodular infiltration of the pancreas.

The spleen weighed 400 Gm. It was fairly firm in consistency. The capsule was thickened, and the organ was a pale, reddish gray. Three small anemic infarctions, with surrounding hemorrhagic zones, were present. The parenchyma was a pale, reddish gray and had a soft consistency. The pulp could be scraped easily, and the details of the follicles were hard to discern.

The suprarenals were normal.

The capsules of the kidneys could be stripped easily. The color was exceedingly pale buff, and there were numerous scattered small and large hemorrhages, some of which were raised and nodular and had white centers. On section, the cortex was of normal width, and the corticomedullary zone was markedly congested. Several of the surface hemorrhages extended in wedge form toward the medulla. The pelves and ureters were normal. The bladder presented several submucosal hemorrhages in the region of the trigon.

The uterus was infantile. The adnexae were normal.

The esophagus near the cardiac portion of the stomach presented two shallow ulcers about 5 mm. in diameter, and also two raised hemorrhagic, dry, granular plaques. The mucosa of the stomach in the cardiac region was flecked with petechial hemorrhages. The lymphatic tissue showed nodular hyperplasia, giving the mucosa a cobble-stone appearance. Peyer's patches and the solitary follicles throughout the gastro-intestinal tract were hypertrophied. The submucosal lymphatic tissue of the appendix appeared diffusely hyperplastic.

Transection of the left humerus revealed a soft, grayish-red, cellular marrow in the epiphysis as well as in the shaft. From the midportion to the epitrochlear condyles, the periosteum was lifted and reduplicated into three or four calcified layers, between which a tissue corresponding in appearance to the marrow was present. The rib marrow was soft, increased in quantity and grayish red. Cross-section of a vertebra and of the sternum revealed beefy-red, soft marrow.

Enlarged lymph nodes were found in the supraclavicular, axillary, inguinal, cervical, mediastinal, mesenteric, retroperitoneal, omental, perigastric, peripancreatic and hepatic and splenic hilar regions. The appearance of these glands was quite uniform. They were globular, discrete, freely movable in their surrounding tissue and soft. The capsule was thin, and on section retracted readily. The cut surface was grayish yellow, and in some of the nodes hemorrhagic areas could be seen. The appearance was homogeneous, and no follicular structure or fibrous areas could be discerned.

Histologic Examination.—At the closing margin of the posterior mitral leaflet, there was a thrombotic verrucous lesion with early organization in the form of palisades of young connective tissue cells. The left auricular endocardium was edematous, but no MacCallum lesion was present. There were leukemic infiltra-

tions in the pericardium. The apex of the ventricular myocardium showed some interstitial scarring. All vessels were engorged with leukemic blood cells, and several hemorrhagic, leukemic infiltrations were seen. Many young Aschoff bodies and a few perivascular scars were present (fig. 4).

In the lungs were confluent pneumonic areas. The alveolar exudate consisted of polymorphonuclear cells and fibrin, despite the engorgement of the local capillaries with leukemic cells. Many of the alveolar walls were necrotic. Bronchi contained purulent exudate. No Aschoff bodies were seen.

Periportal fields showed broad anastomosing channels of leukemic infiltration which pervaded the entire section. The sinusoids were distended with leukemic blood cells. The Kupffer cells did not show any increase in number or changes in form. The capsule was thin and diffusely infiltrated. There were several areas of atrophy of the central cords of the liver with marked fatty change.

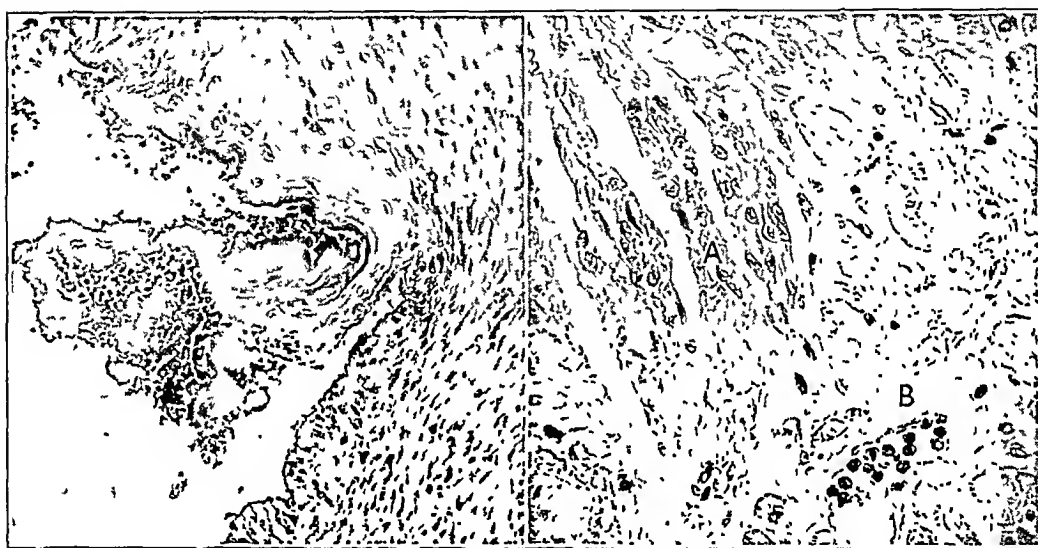


Fig. 4.—Photomicrographs showing histologic changes in the heart. On the left is a section of the posterior mitral leaflet showing verruca with superficial thrombotic mass and palisading of young connective tissue cells. On the right is a section of the myocardium showing large, young Aschoff body (*A*), and blood vessel containing leukemic cells (*B*).

Within the follicles of the spleen, central depletion was seen with some hyalinization of the capillary walls and pyknotic nuclear changes. The lymphatic tissue of the follicles consisted almost exclusively of small lymphocytes. Immature granulocytes were not present, and there was a sharp differentiation between lymphatic tissue of the follicle and the extensive leukemic infiltration of the pulp. The pulp was extremely cellular, the cells consisting of lymphatic cells and granulocytes in various stages of maturity. The sinuses could be made out distinctly in areas, and the endothelium of the sinus did not show any significant alteration. Several of the splenic veins in the trabeculae showed subintimal infiltration.

Diffuse infiltrations, which surrounded individual glomeruli and tubules, were present in the cortex of the kidney. Some of these infiltrations assumed a nodular form. There was also a wedge-shaped area of necrosis, at the apex of which a thrombosed vein was present. Infiltrations were also present around the arcuate

arteries and in scattered areas in the medulla. Glomerular capillaries were frequently seen to contain leukemic blood cells.

Portions of the pancreas were so extensively infiltrated by leukemic cells that the parenchyma was completely obliterated. In other areas, the acini were separated by broad zones of infiltrate. The ducts and vessels were normal. The islets showed no significant change.

The sinusoids of the suprarenals contained leukemic blood.

The parenchyma of the thymus appeared markedly hyperplastic, and normal corticomedullary zones were no longer recognizable. Evidence of extramedullary myelopoiesis could be found in the cellular constituents.

The mucosal lymphatic tissue of the appendix had lost its normal follicular character, and there was a dense infiltration of the mucosa and submucosa by leukemic cells.

Section of a Peyer's patch in the small intestine revealed extensive hypertrophy and the presence of many myeloid cell types.

The spinal cord was normal.

Sections of the small lymph nodes revealed a thin unfiltrated capsule and partially altered structure in which elements of original architecture, such as marginal and medullary sinuses, could still be discerned. There was, however, a uniformity of cell distribution which in no wise suggested the normal distinctions of cortex medulla and secondary follicles. The cell types present revealed a striking loss of the original small lymphatic types, and, while some of these still remained, the predominating forms were those of the granulocytic series; the largest proportion were very immature; many of them were fixed, mesenchymal cells, many corresponded to hemocytoblasts, and numerous eosinophilic and neutrophilic granular derivatives were present. An occasional megakaryocyte was encountered. Frequent mitoses were seen in the free cells. The blood vessels and lymphatics contained leukemic cells.

A longitudinal section of periosteum revealed from five to six flat layers of osseous tissue showing typical bony lamellae and lacunar spaces. Between these were flat layers of leukemic cells compactly arranged, and showing streaming of cells, probably due to pressure. Several bony trabecular connections were seen between the various osseous layers. A cross-section of the shaft of the humerus revealed a marked widening of the haversian and volkmann canals, the lumens containing not only blood vessels, but also large aggregations of leukemic infiltrate. The parallel surface lamellae of the cortical substance were well defined and showed no alteration in the nature of separation or splitting. Examination of longitudinal and cross-sections of the shaft revealed a predominantly longitudinal arrangement of the new bony lamellae. The periosteum was seen outside the most peripheral bony lamellae and between these two, as well as in the striated muscle peripheral to the periosteum, leukemic infiltrate was present.

From a study of these areas and from the irregular arrangement of the reduplicated subperiosteal bony trabeculae, it was possible to determine that these reduplicated layers represented new formation and did not arise by the splitting away of the superficial layers of the cortical lamellae.

Résumé of Case.—The patient, a white girl, aged 11½, was admitted to Lebanon Hospital on Aug. 24, 1932, with a painful, tender swelling of the lower half of the left humerus, which the roentgenogram revealed to be a marked thickening of the periosteum on all sides of the humerus in

its lower half. Examination of the blood revealed a negative Wassermann reaction. The leukocytes numbered 16,400, with a polynucleosis of 82 per cent. No immature forms were observed.

On October 6, following a tonsillectomy and the extraction of five carious teeth, the patient was readmitted to the hospital with a syndrome of fever and migratory polyarthritis. A diagnosis of acute rheumatic fever was made and supported by the response to therapy and the development of cardiac involvement.

The first evidence of a dyscrasia was disclosed by the persistent high leukocyte count in the presence of a normal temperature. The progressive enlargement of the liver, spleen and lymph nodes, the development of the typical blood picture and, finally, biopsy of a lymph gland, which showed diffuse myelopoiesis, established the diagnosis of myeloid leukemia, and the original diagnosis of rheumatic fever was abandoned.

The autopsy, however, revealed the classic pictures of rheumatic fever in the heart and of a generalized acute leukemic myelosis.

The diagnosis from the biopsy was marked extramedullary myelopoiesis as seen in leukemic myelosis.

The anatomic diagnosis was: (1) "acute" generalized leukemic myelosis with involvement of the lymph nodes, liver, spleen and bone marrow; (2) leukemic infiltration in the kidneys, heart, esophagus, pancreas, small intestine and appendix; (3) ossified periosteal reduplications with intervening leukemic infiltrates in the region of the lower part of the left humerus; (4) acute rheumatic verrucous endocarditis of the mitral valve, and acute rheumatic myocarditis; (5) multiple splenic infarctions; (6) ulceration of the esophagus with leukemic infiltrations, and (7) diffuse bilateral, confluent bronchopneumonia.

COMMENT

It was felt impossible to retain the original diagnosis of rheumatic fever when the subsequent appearance of enlarged liver, spleen and lymph nodes, and positive blood findings established the presence of leukemia. The leukemia appeared to account for all the clinical phenomena, including the electrocardiographic evidences of myocardial damage, which were not of a type considered characteristic of rheumatic fever. These changes and the systolic blow which later appeared were held to be consistent with the diagnosis of leukemia on the theoretical basis of a marked anemia and the possibility of myocardial damage coincident with leukemic infiltration and hemorrhage in the myocardium as part of the generalized process. A further theoretical possibility was the development of a terminal thrombo-endocarditis, such as is not infrequently encountered in cases of leukemia, as well as in other wasting diseases.

The course of events suggests that the onset of the acute infection, in this instance rheumatic fever, served to convert the aleukemic into a leukemic phase, and to generalize and accelerate the leukemic process. The rapidity with which this progressed was remarkable. Perceptible increases in size of the lymph nodes, liver and spleen occurred almost daily, and within a period of one month, heretofore impalpable hemato-poietic structures underwent such enlargement that the liver reached to the crest of the ileum; the spleen descended three or four finger-breadths below the costal margin as well as upward, and large clusters of lymph nodes were palpable in all their normal habitats.

The observation of progressive enlargement of the lymph nodes while the patient remained in the hospital offered the opportunity of establishing a time factor in connection with the histologic picture. Sections of a lymph node, the enlargement of which was known to have dated back for a period of only two weeks, revealed the earliest stages of extramedullary granulopoiesis. Klemperer,⁹ in citing the evidence for the derivation of hemocytoblasts from the cellular reticulum in extramedullary sites in postembryonal life, stated that he has observed in the spleens in two cases of acute myeloid leukemia stages suggestive of transformation of fixed elements into free hemocytoblasts identical with the stages seen in the embryo.

The Aschoff bodies in the myocardium corresponded in all details to the classic forms characteristic of acute rheumatic fever, and their structure corresponded to the earlier stages of the life cycle of the Aschoff body (Gross and Ehrlich,¹⁰ Klinge¹¹). The leukemic infiltrations in the heart and the Aschoff nodules coexisted side by side without apparently exerting any mutual effects (fig. 4).

The pneumonic infiltrations consisted exclusively of mature polymorphonuclear cells, despite the predominant "blast" type of cell in the pulmonary vessels and peripheral blood, a characteristic phenomenon in infections occurring in the course of leukemia, recently commented on by Jaffé.¹²

The degree of periosteal changes observed in the first roentgenogram gives unequivocal proof that the leukemia had existed for some time

9. Klemperer, P.: Relationship of the Reticulum to Diseases of the Hematopoietic System, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 655.

10. Gross, L., and Ehrlich, J. C.: Histological Studies on the Aschoff Body, *Am. J. Path.* **6**:621, 1930.

11. Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus, *Virchows Arch. f. path. Anat.* **279**:438, 1930.

12. Jaffé, R. H.: Morphology of the Inflammatory Defense Reactions in Leukemia, *Arch. Path.* **14**:177 (Aug.) 1932.

before the patient's first admission to the hospital, at which time there were no abnormal cells in the blood smear. The onset of the rheumatic fever can be related to the appearance of generalized manifestations in the joints following her discharge, for which tonsillectomy and dental extractions were performed, and which on roentgen and postmortem examination could not be proved to have occurred on a leukemic basis. Smith³ and others have described cases of leukemia in which the manifestations in the joints, because of swelling, redness and tenderness, of migratory character, were indistinguishable from those encountered in rheumatic fever. Mention may be made of the disappearance of the fever and symptoms in the joints in our patient after the administration of salicylates and amidopyrin. In Smith's case, at a time when the patient was still considered to be suffering with rheumatic fever, the skeletal symptoms showed no response to therapy with salicylates.

Sections of the elevated periosteal layers at the lower end of the left humerus revealed newly formed osseous tissue between which leukemic infiltrations were present. Examination of the lamellar architecture of the underlying cortex revealed completely intact cortical bone. This finding indicates that the osseous layers outside of the cortex arose by the formation of new bone, and not by the splitting away of cortical lamellae by the pressure of leukemic infiltrate (fig. 1). Secondary changes occurring in the bone in the course of leukemia, both lymphatic and myeloid, have been well recognized for many years. Since the original description of Heuck,¹³ in 1879, the majority of anatomic descriptions of alterations in the bone complicating this disease are concerned with osteoporotic and osteosclerotic changes (Mott,¹⁴ Schwarz,¹⁵ von Baumgarten,¹⁶ C. Sternberg¹⁷ and Stephens and Bredeck¹⁸). However, the occurrence of periosteal elevations and so-called "ossifying periostitis," on the basis of subperiosteal leukemic infiltrations, has been reported in a few rare instances. The cases of Smith, Taylor, Karelitz and Poynton and Lightwood contain roentgen evidences and in some cases references to the postmortem recognition of subperiosteal changes of this type.

13. Heuck, G.: Zwei Fälle von Leukämie mit eigenthümlichem Blutrespektive Knochenmarksbefund, *Virchows Arch. f. path. Anat.* **78**:475, 1879.

14. Mott, F. W.: A Case of Spleno-Medullary Leukaemia with Haemorrhage into the Cochlea and Semicircular Canals, Associated with Deafness and Loss of Balance, *Med.-Chir. Tr., Lond.* **83**:209, 1899-1900.

15. Schwarz, E.: Ein Fall von Leukämie mit Riesenzellenembolie und allgemeiner Osteosklerose, *Ztschr. f. Heilk.* **22**:294, 1901.

16. von Baumgarten, P.: Myelogene Pseudoleukämie mit Ausgang in allgemeine Osteosklerose, *Arb. a. d. Geb. d. path. anat. Inst. zu Tübingen* **2**:499, 1899.

17. Sternberg, C.: Leukämie und Osteosklerose, *Ergebn. d. allg. Path. u. path. Anat.* **9**:419, 1903.

18. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, *Ann. Int. Med.* **6**:1087, 1933.

In 1901, von Jaksch¹⁹ described a case of generalized periosteal elevations with ossification, associated with a myelocythemia and an enormous spleen. He considered the periosteal disease primary, and the changes in the blood and splenic enlargement secondary. Schlagenhauer,²⁰ in 1904, reported periosteal changes, similar to those which von Jaksch observed, occurring in a patient with a widely metastasizing carcinoma of the pharynx. He felt that in his case, and also in von Jaksch's case, the periosteal changes were not related to the current disease, and suggested that since similar changes had been observed in cases of arsenic poisoning, and since therapeutic doses of arsenic had been given in both his case and in von Jaksch's case, this may have been the etiology of the periosteal change. In 1905, Carl Sternberg, in discussing von Jaksch's case, expressed the view that it was really a leukemia and should be classed with Hueck's and Schwartz' cases as a leukemia with secondary changes in the bone. In 1908, Fabian²¹ mentioned the occurrence of periosteal lymphomas in large cell lymphatic leukemia. Similar tumor masses have been repeatedly described in chloroma, but nodular masses of this type are quite distinct from the diffuse, flat infiltrations with which we dealt. The only other reference to this change which we have been able to discover is that of Geschickter and Copeland,⁸ who mentioned subperiosteal infiltrations in leukemia and who published a roentgenogram showing this change.

The occurrence of subperiosteal elevations due to leukemic infiltration at a time when there was no enlargement of the liver, spleen or lymph nodes and no immature cells in the circulating blood would indicate that coincident with the rheumatic infection there was not only an invasion of the circulating blood by immature cells, but also a generalization of the hematopoietic activity of the reticulum cells of the various organs, which, until that time, was more or less localized to the periosteal elevation observed by roentgenographic examination and perhaps to other restricted foci in the body. These facts throw some light on the manner of origin and progress of a leukemia and on the nature of so-called "acute leukemia."

The published differential diagnoses of periosteal elevation and periosteal ossification, which include healed fractures, trauma without fracture, osteomyelitis, syphilis, tuberculosis, typhoid, leprosy, pulmonary osteo-arthritis, osteitis deformans, rickets, scurvy, chronic icterus, arsenic and phosphorus poisoning and tumors of the bone

19. von Jaksch, R.: Multiple Periostaffection und ein myelogene Leukämie mahnender Blutbefund, *Ztschr. f. Heilk.* **22**:259, 1901.

20. Schlagenhauer, F.: Ueber diffuse ossifizierende Periostitis, *Ztschr. f. Heilk.* **25**:364, 1904.

21. Fabian, E.: Ueber Leukämie besonders ihre grosszellige lymphatische Form, *Centralbl. f. allg. Path. u. path. Anat.* **19**:49, 1908.

(Teleky,²² Beutenmüller,²³ Obermayer,²⁴ Giles and M. Sternberg²⁵), do not mention leukemia, and it would appear from our experience and a survey of the literature that this disease should be considered when such periosteal changes are observed clinically and by roentgenographic study, even in the absence of positive blood and physical findings.

SUMMARY

1. A case of "acute" myeloid leukemia which presented the clinical picture of acute rheumatic fever during an aleukemic phase, and which at autopsy presented the anatomic evidence of both diseases, is reported.

2. The occurrence of periosteal changes in the left humerus at the beginning of the clinical course was found at autopsy to have occurred on the basis of repeated subperiosteal leukemic infiltrations with secondary ossification in layers.

3. A review of the literature of the changes in the bone in leukemia and study of our case result in the inclusion of leukemia in the differential diagnosis of periosteal elevation and ossification.

22. Teleky, L.: Beiträge zur Lehre von der Ostéoarthropathie hypertrophiante pneumonique, Wien. klin. Wchnschr. **10**:143, 1897.

23. Beutenmüller, H.: Toxigene Osteoperiostitis ossificans bei chronischem Icterus, Berl. klin. Wchnschr. **45**:1001, 1908.

24. Obermayer, F.: Knochenveränderungen bei chronischem Icterus, Wien. klin. Rundschau **11**:645, 1897.

25. Sternberg, M.: Vegetationsstörungen und Systemerkrankungen der Knochen, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1899, vol. 7, sect. 2, pt. 2, p. 72.

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